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New trends in biotechnological applications of photosynthetic microorganisms

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Abstract:

As a source of several valuable products, photosynthetic microorganisms (microalgae and cyanobacteria) have many applications in biomedical, electrochemical, and urban-space fields. Microalgal and cyanobacterial (photoautotrophs) implementations have been the subject matter of several reviews, which mainly focused on exploring effective methods of their harvesting, optimal cultivation conditions, energy conversion efficiency, and new strategies for microalgal health-promoting compound recovery. This review highlights recent investigations into biomedical, urban, environmental, and electrical engineering microalgae and cyanobacteria applications over the last seven years. A brief historical outline of advances in photoautotroph-based technologies is presented prior to an exploration of the important role of these microorganisms in combating global warming and food and energy insecurity. Special attention is given to the photosynthetic oxygen production of algae and the possibility of treating hypoxia-associated diseases such as cancer or tissue injuries. Photoautotroph applications in microrobotics, drug delivery and wound healing systems, biosensors, and bioelectronics are also introduced and discussed. Finally, we present emerging fabrication techniques, such as additive manufacturing, that unleash the full potential of autotrophic, self-sufficient microorganisms at both the micro- and macroscales. This review constitutes an original contribution to photoautotroph biotechnology and is thought to be impactful in determining the future roles of microalgae and cyanobacteria in medical, electrical, or urban space applications.

1. Introduction: Microalgae Research Outlook

Microalgae form a diverse group of photosynthetic organisms living in almost all of Earth's ecosystems and ecological niches, like lichens (Bertrand et al., 2016) or mineral springs (Millan et al., 2020); most microalgae are, however, present in freshwater or marine aquatic habitats. Microalgae are of significant ecological and economic importance. They have been identified as a source of almost 50% or 50 gigatons of total organic carbon each year (Hallmann, 2019). Furthermore, these microscale organisms are responsible for CO_2 sequestration with approximately tenfold higher efficiency than that of the plants that grow in terrestrial habitats (Sathasivam et al., 2019). One of the most remarkable advantages of these organisms is their ability to synthesize and accumulate valuable compounds, such as lipids, proteins, carbohydrates, and bioactive molecules with pharmaceutical applications while requiring minimal external resources (Mimouni et al., 2012). Due to this feature and the wide diversity of microalgal species and relatively easy cultivation, in the last 70 years, they have become attractive for a wide range of application, most prominently in the fields of biofuels, functional foods, biopharmaceuticals, and cosmeceuticals. A historical graph of the most crucial milestones in the development of microalgal research is presented in **Figure 1**. One of the first pilot-scale applications of microalgae was in the early 1950s in a wastewater treatment plant, University of California, USA, where scientists cultivated algae to purify sewage (Gotaas et al., 1954). Microalgae played an essential role in wastewater treatment by removing both organic and inorganic pollutants and by oxygenating waste streams for aerobic microorganisms. At the same time, due to the rapid increase in the world's population after World War II and speculations regarding uncertainties in protein supply, microalgae biomass appears to be a high-potential alternative to traditional commodities, such as soybeans, rice, or meat in the global food market. The culture of microalgae as alternative protein and food sources started in the 1950s simultaneously in the USA, Japan and England, followed a little later by Israel, Sweden, and Italy (Borowitzka, 2018). The commercial production of microalgae mass started in the early 1960s in Japan with the culture of *Chlorella* (Borowitzka, 1999). It was followed by commercial culturing of cyanobacteria *Arthrospira* instead of eukaryotic photosynthetic microorganisms in Lake Texcoco by Sosa Texcoco S.A. (Mexico City, Mexico) and expanded to the US, Israel, and Germany between the 1970s and 1980s (Camacho et al., 2019). Indeed, by the 1980s, the production of algal biomass was more than 1000 kg per month in Asia alone (Spolaore et al., 2006). Simultaneously, in the 1970s expanded screening of microalgae and cyanobacteria cultures confirmed that these organisms are not only "nutritional" but also rich in numerous bioactive compounds, such as antioxidants, amino acids, polysaccharides, OMEGA 3 and 6 fatty acids, vitamins (e.g., A, B_1, B_2, B_6, B_{12}, C, E, biotin, folic acid, pantothenic acid), chlorophylls, carotenoids, and phycobiliproteins that are essential for human and animal health (Borowitzka, 2018) as humans and animals cannot synthesize most of them themselves. These molecules are valued for their anticancer, antihypertension, immunomodulatory, antibacterial, anti-inflammatory, or antifungal specific activities, among others (Hamed, 2016). Current trends in the global market show that the demand for natural, bioactive, nutritional, and functional ingredients leads to the development of innovative functional food, cosmetic, and pharmaceutical products.

Fig.1.

Another significant application of microalgae, which is currently rapidly developing, is associated with their use in the production of renewable energy. Increases in petroleum prices, depletion of global reserves of fossil fuels, and global concerns regarding greenhouse gas emissions have led to the extensive exploration and development of alternative, renewable energy technologies such as hydropower, wind, solar, and geothermal, or biofuels (Heshmati et al., 2015). Four major kinds of renewable biofuels may be produced from microalgal biomass, namely methane by anaerobic digestion, biodiesel by trans-esterification or hydro-esterification of (algal) lipids, bioethanol by fermentation of (algal) carbohydrates, and biohydrogen by photobiological reactions (Hamed, 2016; Okoro et al., 2017). The potential of microalgae as an energy source was extensively explored in the early 1980s due to a pioneering initiative named the 'Aquatic Species Programme (ASP)' (US), which attracted research interest in both theoretical and commercial realms (Borowitzka and Moheimani, 2013). The high potential of microalgae as a source of renewable energy is related to specific microalgae features. For instance, when compared to terrestrial plants, the algal productivity index is twice as high. After the 1990s, microalgal biotechnology entered a new era, mainly due to the genetic engineering of microalgae species (Fu et al., 2019). The molecular biology and transformation approach used for algal genetic engineering have shown potential in creating desired high-performance microalgae species and improving the yield and quality of valuable microalgae biomolecules. Nowadays, one of the most preferring technology for algal genome engineering is the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9), due to its high specificity, simplicity, and higher versatility compared to e.g. sequence-specific recombinant nucleases including zinc-finger nuclease (ZFN) or transcription activator-like effector nuclease (TALEN) (Patel et al., 2019; Shin et al., 2016). Since 2014, CRISPR-based genome editing techniques have been used to manipulate the genetic material of some freshwater and marine microalga (Wenzhi et al., 2014; Nymark et al., 2016; Naduthodi et al., 2021). However, there are still many concerns regarding the introduction of Genetically Modified Organisms from the laboratory to the natural environment, mainly due to possibilities of unpredicted gene flow in the natural habitat (Fayyaz et al., 2020). After an in-depth, long-term research, new regulations may need to be implemented to overcome the constraints and limitations in this promising area.

Microalgae have been intensively examined and developed as a source of renewable biomass and health-promoting bioactive compounds. As illustrated in **Figure 1**, between the years 2000 and 2021, there was a ~7-fold increase in the number of publications in the area of microalgal research. Most of the review papers published in the past ten years provided insight regarding new solutions in bioenergy production based on these phototrophic organisms (Goh et al., 2019; Günerken et al., 2015; Markou and Nerantzis, 2013; Rawat et al., 2013; Salama et al., 2017; Yin et al., 2020). Researchers have also focused on recent developments and perspectives on microalgal cultivation and harvesting techniques to enhance the accumulation or extraction of high-value metabolites it may happen. In most of the review literature, microalgae serve as an efficient source of valuable metabolites or biomass for nutritional, medical, or bioenergetic purposes (De Jesus Raposo et al., 2015; Manirafasha et al., 2016; Rizwan et al., 2018; Sathasivam et al., 2019; Xu et al., 2012). However, in the last few years, new trends in microalgae-based systems have been observed. **Figure 2** presents a timeline of the novel advances in applications of living photoautotrophs cells. These include, microalgae use in tissue engineering (Haraguchi et al., 2017), biohybrid magnetite microrobots (Yan et al., 2017), bioinspired multifunctional therapeutic tools (Qiao et al., 2020), personalized drugs (Delasoie et al., 2018), 3D-printed biophotovoltaic systems (Sawa et al., 2017), bionic 3D-printed coral reefs (Wangpraseurt et al., 2020), and "algal window" or Bio Intelligent Quotient (BIQ) houses. This seeks to provide an account of current advances in microalgal biotechnology while simultaneously exploring new strategies that involve photosynthetically active, unicellular algal applications in biomedicine and health care, electrochemistry, and urban space. This work comprises an original contribution to mostly live microalgal biotechnology. We have mainly focused on eukaryotic microalgae; however, the remarkable application examples of cyanobacteria have also been mentioned. Because cyanobacteria are sometimes called blue-green microalgae and are microsized, they are commonly named "microalgae". However, it is worth remembering that cyanobacteria are a group of prokaryotic bacteria while microalgae are small eukaryotic organisms.

Fig.2.

2. Systems for Human Health

2.1. New precise medical therapeutic devices/microcarriers

Conventional drug administration methods and techniques for detecting severe diseases have limitations that adversely affect patients' quality of life. The main reasons for this are unfavorable pharmacokinetic properties of therapeutics, such as short half-lives, limited biodistribution, and poor body retention. Hence, repeated administration at high doses is necessary to produce the desired therapeutic effect, which may lead to increased toxicity and side effects (e.g., cardiotoxicity, myelosuppression, or induced vomiting with nausea) (Avila et al., 2019; Epstein et al., 2020). Advances in the development of new micro/nanotools in medical therapies, therefore, seek to circumvent the issues mentioned above by enhancing the selectivity and targeted delivery of diverse cargoes to diseased cells while also limiting damage to healthy tissues. Such advancements can reduce the global patient burden, especially in cancer treatment. Currently, this cell-specific targeting can be accomplished by attaching pharmaceutics and inorganic therapeutics to specially designed carriers such as liposomes, dendrimers, and metallic or nonmetallic nanoparticles (Natarajan et al., 2014). Since the synthesis of such materials is expensive, time-consuming, polluting, and may require toxic chemicals (Maher et al., 2018), a need arises to design nontoxic, effective, and biocompatible carriers by means of green chemistry methods. In recent decades, attempts have been made to develop bioinspired multifunctional therapeutic tools based on unicellular eukaryotic microalgae (Hussein and Abdullah, 2020; Terracciano et al., 2018).

Literature examples of microalgae applications as microcarriers are presented in **Table 1**.

Tab.1.

The notable study of biobased microcarriers based on microalga diatom (*Aulacoseira* sp.) frustules, a natural, biocompatible, and inexpensive biosilica was undertaken by Losic et al. (2010) (Losic et al., 2010). Bariana et al. (2013) and Wang et al. (2013) also employed diatoms frustules as drug delivery systems. (Bariana et al., 2013; Wang et al., 2013). The great interest in these biomaterials as microcarriers arises from their hierarchical 3D silica porous structures (shells) which is characterized by species-specific patterns and pore sizes in the range of 2 µm to 2 nm, as shown by Van de Vijver (2021). The porous architecture of these diatoms frustules makes it possible to load therapeutics both on the surface and inside the biosilica shell, thus, significantly influencing the kinetics of the release of the active substances (Aw et al., 2012). Given that the size of diatoms frustules is comparable to that of cancerous cells (≈10 µm), these frustules cannot cross the cancerous cell membrane. Nevertheless, it is assumed that they may deliver cargoes in the vicinity of the targeted tissue and release the active substances with high efficiency (Delasoie et al., 2018), which is why the latest trends are mainly associated with chemical modification of the diatom frustules surface to obtain safe, functional carriers with high efficiency relative to unhealthy tissue. These chemical modifications are possible because the surface of the frustule possesses reactive Si-OH groups that can be easily functionalized (electrostatically, covalently, or by cross-linking) with polymers, nanoparticles and (soluble/insoluble) therapeutic molecules and tumor targeting agents (**Table 1**) (Briceño et al., 2021; Delasoie et al., 2018; Kumeria et al., 2013; Losic et al., 2010; Vasani et al., 2015).

To ensure the selectivity of microcarriers against the unhealthy tissue, Delasoie et al. (2018) proposed a new type of bioinspired drug delivery system (Delasoie et al., 2018), where the *Aulacoseira* sp. frustule was modified with cyanocobalamin (vitamin B_{12}) (a tumor-targeting agent). Since the rapid proliferation of colorectal cancerous cells leads to an enhanced demand for vitamin B_{12} compared to the vitamin demand by the surrounding (normal) tissues, the modification improved the attachment of the microshuttle to tumor tissues via TC(II)–R (transcobalamin II receptor) and permitted the slow release of chemotherapeutic drugs to the targeted site. In another research (Delasoie et al., 2020), they showed that linking the photoactivable units of porphyrins to vitamin B_{12} (**Figure 3A**) can sensitize the tumor and lower the total drug dose required for effective treatment (by generating CO and $^1O_2$ with light irrigation). This targeted drug delivery strategy combined with selective spatial-temporal light activation decreased cancerous cell survival from approximately 40% to ca. 20%. These findings were indicative of the future potential for more effective and noninvasive treatment therapy for colorectal cancer, the most common and recurrent tumor in humans (Perera et al., 2012). However, more studies are needed to develop a coating formula to ensure the exposure of active substances in the tumor only, especially in oral drug delivery systems.

Fig.3.

Usually, diatom frustule surface modification requires the use of organic solvents and covalent crosslinkers which make the whole system less biocompatible. To overcome this issue, Delalat et al. (2015) (Delalat et al., 2015) incorporated the IgG-binding domain of protein G onto the surface of the diatom of *Thalassiosira pseudonana* without the use of additional chemicals. For this purpose, the authors constructed the S-T8-GFP-GB1 fusion gene by recombinant DNA technology and incorporated it into the diatom genome. *In vivo* tests confirmed that the antibody-labeled GB1 diatom biosilica shell loaded with hydrophobic anticancer drugs, camptothecin and 7-ethyl-10-hydroxycamptothecin, reduced tumor volume by ~50% after the administration of a single dose. Moreover, biodistribution analysis showed that degraded *Thalassiosira pseudonana* biosilica was found in the kidney and liver but not in other organs such as the brain, heart and lung. It was also demonstrated that these naturally occurring, nonexpensive porous silica-based structures could replace synthetic silica particles in pH/thermoresponsive-controlled drug delivery systems for various therapies, including cancer treatment. To improve the delivery of the anticancer agent doxorubicin (DOX), Sasirekha et al. (2019) grafted chitosan molecules onto the pretreated surface of *Amphora subtropica* frustules (**Figure 3B**) (Sasirekha et al., 2019). The formed chitosan layers acted as pH-responsive nanovalves to regulate the dosing of drugs in tumor tissue. The prepared platform based on *Amphora subtropica* frustules with a high drug load (~90%) was biodegradable and biocompatible. Crucially, *in vitro* studies showed that the slow release of DOX from carriers has an augmented cytotoxic effect against the immortalized lung cancer cell line compared to free DOX.

In addition to diatom frustules, living photoautotrophic cells can effectively deliver drugs to tissues and body cavities, especially those attacked by cancer. Since the cell membrane of the *Spirulina platensis*, is rich in channels and junctional pores (14–16 nm), it was possible not only to adsorb positively charged DOX molecules on the negatively charged cell membrane but also to encapsulate inside cyanobacteria (molecules enter the cell envelope), resulting in high efficiency of drug loading (85%) (Yan et al., 2019; Zhong et al., 2020a). Additionally, DOX release was pH-sensitive and the best values were observed at acidic pH (5.5), which is important in cancer treatment. A similar way to load small molecules and proteins (passage across cell wall and membrane barriers) was observed for green microalgae *Chlamydomonas reinhardtii* (Hyman et al., 2012). Additionally, Shchelik et al. (2020) showed that antibiotics (vancomycin) could be effectively bonded to the surface of *Chlamydomonas reinhardtii*, developing a new drug delivery system that can become a safer alternative to the use of nanoparticles since it does not trigger an immune response and limits the risk of increased bacterial resistance (Shchelik et al., 2020). Notably, chlorophyll autofluorescence gives microalgal-based carriers excellent capability for noninvasive tracking and real-time *in vivo* monitoring (Zhong et al., 2020a). However, the remote control over microalgal motion within the body presents difficulties. In an attempt to solve this issue, living cells are physically combined with various artificial structures and materials into a biohybrid microcarrier.

Microrobots

Microrobots, also called microswimmers, are living microcarriers with photosynthetic microorganisms actuators powered in various ways (magnetic field or light beams) with high propulsion velocities and phototactic guidance capabilities (Xie et al., 2016). Based on the data collected in **Table 2** *Spirulina platensis* and green microalgae *Chlamydomonas reinhardtii* are currently predominantly used for this purpose.

Table 2

Spirulina platensis has gained extensive interest due to the „tunability" of its morphological features such as the helical angle, helix diameter, and body length (Gao et al., 2014; Yan et al., 2015). Indeed, the spiral morphology and corkscrew motion of *Spirulina platensis* enables its use as a microswimmer to transport therapeutics to the pulmonary capillaries (**Figure 4A and B**) or in neuronal regenerative therapies, as shown by Zhong et al. (2020a) and Liu et al. (2020), respectively (Liu et al., 2020; Zhong et al., 2020a). In turn, the green microalgae *Chlamydomonas reinhardtii* with a diameter of ca. 10 μm possess flagella, allowing for motion along a random spiral path in the absence of external controlling forces (Xie et al., 2021; Xin et al., 2020). Notably, Xin et al. (2020) showed that the motion of microalgae could be controlled by optical force. To achieve this, the authors built standard optical tweezers of a continuous-wave solid-state laser beam around an inverted optical microscope (operating at λ=1064 nm). Thanks to this, they could generate an optical trap acting as a pivot. To control the trap, the group used an acousto-optic deflector system as a spatial light modulator. In effect, by adjusting the optical power of the annular scanning trap and the central trap, it was possible to change flagella beating to rotary motion about the focal spot, clockwise or counterclockwise. Xie et al. (2021) revealed that *Chlamydomonas reinhardtii* could be employed in transporting functionalized PS (polystyrene) beads from one place to another, and the trajectories of most cells with the beads were consistent with the direction of the light source (λ = 500 nm), while also showing good directionality (in the x-direction) (Xie et al., 2021). Alkolpoglu et al. (2020) on the other hand presented a completely different approach that was based on the creation of a thin and soft layer of a natural polymer, containing iron oxide nanoparticles, around the algal cell (Akolpoglu et al., 2020). The authors observed that such a biohybrid could be steered in a controlled manner toward the light. The presence of the nanoparticles enables the loading of DOX (by a photocleavable linker) to achieve light-triggered drug release. *Chlamydomonas reinhardtii* showed the ability to deliver large cargoes and destroy biological aggregates, including *in vitro* blood clots. The issue is the hypoxic environment in tumors, which reduces the effectiveness of radiotherapy (RT) and photodynamic treatment (PDT) (Jing et al., 2019). To increase the oxygen level locally, Qiao et al. (2020) presented an innovative method of *in situ* O_2 generation in a mouse tumor under photosynthesis induced by red light (**Figure 4C**) (Qiao et al., 2020). The authors utilized *Chlorella vulgaris* to produce a large amount of chlorophyll. *Chlorella vulgaris* was subsequently modified via coating a red blood cell layer (RBCM) with the cryogenic ultrasonication method. The coating of the microalgae with the RBCM layer facilitated the reduction of macrophage uptake, thus aiding the systemic clearance of the algal for enhanced algal metabolic activity, which led to the improved delivery of *Chlorella vulgaris* to tumor tissues. The combination of the photosynthesis of the modified microalgae with radiotherapy and photodynamic treatment enhanced apoptosis of cancer cells and led to tumor regression in mice. Similar combined RT/PDT therapy based on microalgae was also proposed by Li et al.(2020) (Li et al., 2020) and Zhong et al. (2021b) (Zhong et al., 2021b). Here, in comparison to Qiao et al. (2020), the authors presented low-cost and easier methods of *Chlorella vulgaris* surface modification to enhance the biocompatibility of biohybrids. They covered the microalgae surface with non-immunogenic and environmentally friendly biomaterials commonly used in medicine, such as silica (Li et al., 2020) and calcium phosphate (Zhong et al., 2021b). Thanks to this, it may be more reliable to produce such biohybrids on a large scale, which will allow the replacement of the current therapies with this innovative method of cancer treatment.

Fig.4.

The above reports highlight new opportunities to fabricate live, intelligent, multifunctional microrobots for medical applications. One solution is to control the trajectory of microalgae movements with the optical force that is exerted from the attraction and repulsion of light beams. This could be problematic in hard-to-reach regions (e.g., deep organs), where fluorescence-based imaging and steering by phototaxis may not be effective due to reduced penetrance. To overcome this challenge, microrobots with decorated surfaces have been constructed as tools for targeted drug delivery and minimally invasive microsurgery. A simple strategy to guide the microrobot in hard-to-reach regions is magnetizing the algae with Fe_3O_2 nanoparticles (Yan et al., 2017). For instance, these authors were able to show that the thickness of the magnetic nanoparticles employed in preparing magnetized *Spirulina platensis* via facile dip-coating could be easily controlled (Yan et al., 2017). The authors showed that with the imposition of an external magnetic field and magnetic resonance imaging, the motion of a swarm of microrobots consisting of *Spirulina platensis* inside such a complex organ as rodent stomachs in *in vivo* tests could be controlled and tracked. Xie et al. (2020) used a similar technique via coating the magnetic microswimmer based on *Spirulina platensis* with polydopamine to enable microrobot tracking due to the enhanced photoacoustic signal of the polydopamine layer (Xie et al., 2020). Next, Zhong et al. (2020b) showed that *Spirulina platensis* coated with superparamagnetic magnetite can also be used as a microrobotic platform for efficient production of O_2 (ameliorating tumor hypoxia) and for the generation of cytotoxic reactive oxygen species (ROS) upon laser irradiation (Zhong et al., 2020b). This may significantly contribute to the RT/PDT efficiency in the treatment of hypoxic solid tumors. Liu et al. (2020) also proposed a promising solution for patients with neurotrauma and neurodegenerative diseases. The authors utilized *Spirulina platensis* to fabricate biodegradable, multifunctional micromotors for precise neuronal regenerative therapies by coating the cyanobacteria with magnetic Fe_3O_4 and piezoelectric $BaTiO_3$ nanoparticles (**Figure 4D**) (Liu et al., 2020). A magnetic field could precisely control the movement of such a biohybrid to reach a single-cell target. Then, due to the piezoelectric effect, the stimulation of neural cells could be induced.

To avoid any disruption in the green microalgae flagella propulsion, different methods of magnetizing *Chlamydomonas reinhardtii* have been proposed. For instance, Santomauro et al. (2018) magnetized *Chlamydomonas reinhardtii* by accumulating terbium (Tb^{3+}) in the microalgae cells. In this study, the Tb^{3+} served as both a magnetizer and a „marker" by its luminescence properties (Santomauro et al., 2018). This solution enhanced the tracking of the microrobots inside the body, e.g., in deep organs, paving the way for a wide range of potential medical applications. Crucially, the authors established that the „swimming speed" of the cells was not affected by Tb^{3+} treatment, and the microswimmers could be navigated in the dark by applying a strong magnetic field. Another method of microalgae magnetization was demonstrated by Yasa et al. (2018), where polyelectrolyte-functionalized magnetic PS microparticles were attached to *Chlamydomonas reinhardtii* (**Figure 4E**) (Yasa et al., 2018).

The authors observed that most algal microswimmers carried at least one or two spherical cargoes and could be guided magnetically in the x-direction. Targeting of the objects of interest was achieved by changing the direction of the applied magnetic fields. However, the motility of the microswimmers was strongly dependent on the location of the attached PS microparticles on the green algal body. The lowest swimming speed was for *Chlamydomonas reinhardtii* with microparticles linked to flagella. Moreover, the biohybrid microswimmers (biogenic microalgae and non-biogenic PS microparticles) were shown to be nontoxic compared to bacteria-powered biohybrid microswimmers and effective in targeting the model therapeutic to cancerous cells. Apart from low cytotoxicity the biohybrid microswimmers powered by *Chlamydomonas reinhardtii* and effective impact of these algal microswimmers fabricated using drug-loaded PS microparticles on cancerous cells, the release of drugs can also be controlled by the stimuli-responsive properties of polyelectrolyte layers.

When microrobots are applied as drug delivery systems, they must be safely removed from the human body. All of these examples showed high biodegradability and low toxicity. For all that, long-term studies are necessary, and algal microswimmers' immunocompatibility should be further investigated *in vivo* to assess their safety. Also, in the case of the therapy with live microalgae or cyanobacteria, it is necessary to know how all biocompounds released *in situ* by these photoautotrophic microorganisms can affect tissue cells. Nowadays, most studies focused only on therapeutic agents and this subject has not been discussed in papers. Another important issue is the precise transportation of the microrobot over long distances to reach the exact target in tissue, followed by the effective release of the active agents. Since such studies are limited, there is a need for further investigation to show whether this innovative treatment method can replace conventional therapies.

2.2. Overcoming hypoxia in tissue engineering

Organ damage and failure represent a crucial health care problem and are among the leading causes of clinical patient deaths globally (Home - GODT, 2019). One of the major challenges in engineered tissues, including brain, cardiac, skin, muscle, or pancreas, is the sustained supply of oxygen and nutrients to prevent critical hypoxia of tissue-engineered constructs during cultivation (Suvarnapathaki et al., 2019; Zhong et al., 2021a), which is called oxygenation (Veloso-Giménez et al., 2021). To resolve the aforementioned issues, recent research has been exploring the development of a new class of multifunctional „breathing" biomaterials that will provide adequate oxygen and vascularization of immobilized cells. These new bioengineered biomaterials must be nonimmunogenic, biocompatible, multifunctional, and exhibit favorable mechanical properties. For instance, in the study by Bloch et al. (2006) "breathing" biohybrid material was developed for the first time by incorporating photosynthetic microorganisms into the engineered bioartificial pancreas. Coculturing of mouse pancreatic islets and microalgae-*Chlorella sorokiniana* opened up new revolutionary opportunities in tissue engineering and regenerative therapies. Oxygen generated by tested microalgae strains compensated the oxygen requirements of encapsulated islets and provided proper insulin secretion (Bloch et al., 2006). Yamaoka et al. (2012) went a step further and proposed a new transplantation protocol based on unicellular *Chlorella vulgaris* microalgae to prolong the viability of rat pancreas after cardiac death (DCD) (Yamaoka et al., 2012). Transplanted organs, especially from donation lapsing into circulatory deficit, are highly exposed to irreversible damage, caused by low oxygen and high carbon dioxide conditions in standard methods, like static cold storage. Yamaoka et al. (2012) created a respiratory system, for DCD organs intended for transplant, based on eukaryotic microalgae *Chlorella* sp. which insures constant gas exchange between rat DCD pancreases and *Chlorella* sp. Researchers successfully transplanted DCD pancreases into rats with STZ-induced diabetes, 3h after cardiac arrest of the donor. In combination with standard methods, e.g. automated perfusion with immersion, the invention may produce a paradigm shift in the clinical transplantation protocols. Even so, without critical analysis of the putative symbiotic relationship between microalgae and mammalian organs or tissue, this innovative strategy will not find its utility in clinical settings. Basic research on the interdependence of a broader spectrum of mammalian cells or tissues and microalgae or cyanobacteria are required. Different photosynthetic microorganisms were investigated by (Cohen et al., 2017) and (Haraguchi et al., 2017) to create oxygen-releasing bioartificial cardiac tissue. Cohen et al. (2017) used the unicellular cyanobacterium *Synechococcus elongatus* to repair rat cardiac tissue after myocardial infarction or coronary artery disease (Cohen et al., 2017). Rat cardiomyocytes were successfully cocultivated with *Synechococcus elongatus* under hypoxic conditions, and oxygen produced by cyanobacteria under an external light source enhanced cellular metabolism. In the second stage, they injected *Synechococcus elongatus* directly into the male rat intramyocardially after model myocardial infarction (**Figure 5A**) and demonstrated that this unprecedented approach might rescue the myocardium from acute ischemia. In cell-based regenerative and tissue-engineered therapies, not only the cellular environment but also culture spatial arrangement may affect the cellular biochemical activity. The three-dimensional (3D) model culture systems surrogate more closely actual tissue, especially in the context of *in vitro* pharmacological or toxicological tests. Nevertheless, 3D engineered tissues without proper vascularization have thickness limitation which is approximately 40-80 µm, due to the hypoxic conditions of the inner thicker artificial tissue systems. To overcome this limitation, Haraguchi et al. (2017) designed three-dimensional, multilayer cell sheet-based cardiac tissue composed of rat cardiomyocytes and the unicellular green microalgae *Chlorococcum littorale* (Haraguchi et al., 2017). The coculture system prevented damage of the cell sheet tissue because algae permanently supply oxygen, reduce ammonia, and improve tissue thickness (created significantly thicker cardiac tissue, approximately 160 µm). **Figure 5B** shows the histological observation of a five-layered rat cardiac cell sheet with and without algae (Haraguchi et al., 2017). As can be seen, microalgae improved multi-cell layered tissue and prevented cell damage. The microalgae species employed for oxygenation in bioartificial tissue engineering are presented in **Table 3**.

Fig.5.

To comprehend the complex cellular interactions in 3D, new techniques to create 3D bioartificial tissue are of great interest. Three-dimensional, artificial, bioengineered tissue provides functionality and may replicate the same native microenvironment of natural tissues, e.g., collagen-based 3D „green skin" created for skin tissue repair (**Figure 5C**) (Hopfner et al., 2014), where fibroblast cells were cocultivated with *Chlamydomonas reinhardtii* microalgae in collagen-based scaffolds. Next, the synthesized biomaterials were studied in *in vitro* tests. The results showed that artificial 3D photosynthetic "green skin" could decrease the hypoxic response in fibroblasts. Another approach that can be applied in the creation of three-dimensional bioartificial tissues is 3D printing (3DP). Remarkable advances have been made in 3DP, enabling the fabrication of precise, functional, and biocompatible three-dimensional scaffolds (Podstawczyk et al., 2021). Among various 3DP technologies, bioprinting has emerged as a new and effective tool for the entrapment of cells, microalgae, or/and active agents. This approach is now widely used in regenerative medicine and artificial tissue engineering. It makes possible a flexible fabrication of living systems with a broad range of shape designs and structural and functional complexities (Shavandi et al., 2020, Mirzaei et al., 2021). In 2015, Lode et al. introduced the term „green bioprinting", which refers to 3D bioplotting of *Chlamydomonas reinhardtii*-embedded alginate-based hydrogel scaffolds (Lode et al., 2015). Using alginate-based material, stable and multifunctional 3D structures could be printed with photosynthetic functions of microalgae. The algae survived the extrusion process and maintained their ability to proliferate (**Figure 5D**). The authors also used cocultures of microalgae and human cell lines to test growing hybrid-tissues *in vitro*. In a subsequent study, Krujatz et al. (2015) investigated *Chlamydomonas reinhardtii* and *Chlorella sorokiniana* microalgal viability and functions under nonoptimal cultivation parameters to optimize coculture conditions (Krujatz et al., 2015). Recently, Zhang's team utilized the ability of *Chlamydomonas reinhardtii* to produce oxygen for mammalian cells within 3D bioprinted vascularized GelMA-based tissues (Maharjan et al., 2021). Vascularization was achieved by cellulase-mediated digestion of the hydrogel to create perfusable and interconnected microchannels that were subsequently endothelialized.

3D bioprintable materials, bioinks, are formed by combining cells and various biocompatible matrix precursor solutions. The selection of scaffolding material is challenging as the bioink should have sufficient viscosity and shape fidelity to allow deposition of high-resolution designed structures and biocompatibility to support cell growth. The diversity of bioink material, the possibility to obtain various geometrical 3D shapes, and microalgal functionalities, make 3D printing an attractive technology for the design of photosynthetic materials for biomedicine. The next generation of photosynthetic bioinks will be designed to be triggered by environmental factors and respond to them. However, the main challenge regarding microalgal living biomaterials is their successful clinical translation. To apply the therapeutic approach that is based on photosynthetic microorganisms into clinical settings, it is crucial to examine their biocompatibility and nonimmunogenicity. Only a few studies have dealt with those aspects so far. For example, Alvarez et al. (2015) injected *Chlamydomonas reinhardtii* into zebrafish embryos (**Figure 5E**) and observed that no substantial immune response of the host occurred after several days of fusion, suggesting that microalgae may be well tolerated as external bodies (Alvarez et al., 2015).

Tab.3.

2.3. Photosynthetic biomaterials - the new generation of wound healing therapy

Chronic wound healing is a common and severe problem for both patients and physicians. The issue of difficult-to-heal wounds affects approximately 0.2–1% of the global population; in Poland, it affects approximately 0.5 million patients (i.e. ~1.3% of the Polish population). The World Health Organization (WHO) suggests that the number of patients suffering from chronic wounds in developed countries will increase due to the rise of the global geriatric population from 84.0 million in 2014 to 2.0 billion by 2050 (Grand View Research, 2021). Therefore, it is a considerable health and social issue (Schreml et al., 2010). The standard of care for chronic injuries is still insufficient and new solutions are constantly being sought (Gray et al., 2018; Nizioł et al., 2021). Given that microalgae or cyanobacteria are a rich source of healing-promoting ingredients such as fatty acids, carotenoids, xanthophyll pigments, vitamins A, B_1, B_2, and $B_{12,}$ and amino acids, they may be employed in facilitating skin regeneration (Elbialy et al., 2021; Pandurangan et al., 2021). Microalgae are also hypoallergenic and can be safely applied directly to the skin (Obaíd et al., 2021). Due to these favorable properties, algal extract-based wound dressings are currently commercially available, with innovative solutions in this field constituting great interest to both the academic and industrial sectors.

The most common chronic wounds are ulcers and diabetic feet. In addition, wounds caused by burns need an appropriate form of treatment to avoid complications such as scarring, discoloration, or joint contractures. Thus, based on the wound type, suitable dressing material and structure must be used that creates a moist wound and protects it from contaminants. For instance, Jung et al. (2016) proposed an innovative solution based on the development of a polycaprolactone (PCL) nanofiber mat loaded with *Spirulina platensis* extracts (Jung et al., 2016). The results showed that *Spirulina platensis* aqueous extract accelerated the rate of skin wound regeneration and reduced reactive oxygen species levels in cells by increasing cellular resistance to ROS, even though the extract was embedded in PCL nanofiber. Therefore, this hybrid nanofiber/*Spirulina platensis* extract material may be applied in clinical therapies, though further follow-up studies are needed to confirm the efficacy of the above-mentioned dressings. Green microalgae can also be a valuable source of compounds helping in wound curing as demonstrated by De Melo et al. (2019). The research group tested hydrogel-based materials containing different concentrations of *Chlorella vulgaris* extracts directly on wounded mice (de Melo et al., 2019). The microalgae extract that was rich in steroids, triterpenes, saponins, and sugars, and exhibited phytochemical, antioxidant, antibacterial, and antifungal activities, accelerated wound healing as compared to the control group. Still, before clinical applications, any biomaterial should be tested for immunogenicity. Future research on microalgal extracts should concentrate on *in vitro* and *in vivo* tests for finding out algal compounds that can potentially provoke an immune response when applied directly to the wound.

Despite the many advantages shown in the above examples, materials based on microalga extracts cannot provide oxygen to the wound site, which is necessary for effective skin regeneration (Chávez et al., 2016). To address this challenge, Chen et al. (2020) developed a patch filled with 1-mm diameter hydrogel beads containing living cyanobacterium *Synechococcus elongatus* (**Figure 6A**) (Chen et al., 2020). The living biomaterial was embedded between a hydrophilic polytetrafluoroethylene membrane serving as a primer to enable bidirectional gas and water exchange while keeping external inflammatory bacteria out. A polyurethane film was applied to the back of the covering to create a wound-sealing system between the wound and the dressing after adhering to the skin. The study confirmed that patches increased wound oxygenation, fibroblast proliferation, and angiogenesis, and were non-toxic and did not trigger an immune response. Recently, Li et al. (2021) developed bioactive „living hydrogel" based on *Spirulina platensis* to produce and locally deliver oxygen to the wound to alleviate acute and chronic tissue hypoxia (Li et al., 2021). These innovative materials combined with laser irritation make a promising strategy in the treatment of infected wounds. Nevertheless, development of the algae-embedded dressings should also focus on the effects of metabolic substances produced by the micro-organisms, which can adversely affect wound healing.

Biomaterials immobilizing microalgae and cyanobacteria affect their functionality and may themselves play an important role in wound healing. It is, therefore, crucial to select or design the scaffolding material that not only provides a suitable microenvironment for the microorganisms but also supports tissue regeneration. Chávez et al. (2021) seeded cyanobacterium *Synechococcus* sp. PCC 7002 (SynHA) inside a fibrin-collagen hydrogel matrix. A schematic representation of the designed photosynthetic material is presented in **Figure 6B**. The study showed that the photosynthetic capacity of cyanobacteria was sufficient to maintain the proliferation and viability of human cells under hypoxic conditions. The positive effect of photosynthetic oxygen on cell viability was specifically evident when the cells were incubated under hypoxic conditions (Chávez et al., 2021). A comparable study was performed by Schenck et al. (2015), who infused collagen scaffolds with green *Chlamydomonas reinhardtii* microalgae (Schenck et al., 2015). The created hybrid material was implanted directly into full-thickness mouse skin defects. Detailed analyses of the implanted biomaterial revealed a high level of vascularization in the presence of microalgae.

Fig.6.

Genetic engineering opens up new possibilities to improve microalgal oxygen production and transfer to the wound site. Genetic modification of a *Chlamydomonas reinhardtii* strain made it possible to constitutively secrete human vascular endothelial growth factor VEGF-165 (VEGF) and deliver it *in vivo* to injured cells (Chávez et al., 2016). The coding sequence of human vascular endothelial growth factor A (accession number NP_001165097) was aligned with the codon bias of *Chlamydomonas reinhardtii*. Recombinant growth factor production was quantified by ELISA and the rate of secretion into the culture medium was determined to be 28.0 ± 4.38 ng VEGF/ml. To evaluate the biocompatibility of the created photosynthetic biomaterials, the scaffolds were transplanted into wounds placed in the backs of fully immunocompetent mice. No immune response was observed. An interesting solution was also presented by Centeno-Cerdas et al. (2018), where genetically modified *Chlamydomonas reinhardtii* microalgae were used to produce "photosynthetic surgical threads" (Centeno-Cerdas et al., 2018). The authors showed that photosynthetic microalgae could be immobilized in sutures, continuously releasing oxygen and therapeutic recombinant growth factors directly at the wound site. The results of sutures' resistance to damage and mechanical stress confirmed their high potential in future clinical practices. Unfortunately, such materials are not free of limitations. Storage and sterilization of these products, which contain live microorganisms, may be problematic. Further research is required to investigate the safety of their use and to simplify their storage.

2.4. Functional food

Microalgae are considered highly nutritious, innovative, and easily accessible food ingredients. To date, various marine-derived foods have been explored in several review papers (Barka and Blecker, 2016; Bueno et al., 2014; Chacón-Lee and González-Mariño, 2010; Ferrazzano et al., 2020; Matos et al., 2017; Nethravathy et al., 2019). These articles mainly summarize the most valuable microalgal metabolites, their production, applications in the food industry, and innovative microalgae-based food products. Bernaerts et al. (2019) indicated that microalgae can play a structuring role in food, serving as a texturizing ingredient (Bernaerts et al., 2019). The authors highlighted the indisputable role of food processing techniques in acquiring the proper structure of food products.

The global food industry is moving towards mass customization strategies to address individual issues of taste, shape, color, texture, flavor, and nutrition (Mantihal et al., 2020). Current global trends favor sustainable and efficient food production and consumption. In this context, additive manufacturing is likely to revolutionize the future food ecosystem. 3D printing allows for personalized meals based on an individual's biological and genetic makeup, quality of life, health status, and environmental factors. For example, additive manufacturing can help create substitutes for meat and recycle food waste residues. 3D food printing is anticipated to reduce hunger in countries where fresh, nutritious, and affordable food products are inaccessible (Birtchnell and Hoyle, 2014). It seems evident that the combination of microalgae and additive manufacturing should be a functional food science innovation strategy.

To date, 3D printing has been exploited to fabricate microalgae-containing snacks and cookies (Uribe-Wandurraga et al., 2021, 2020; Vieira et al., 2020). Using additive manufacturing, Uribe-Wandurraga et al. (2020) fortified cereal snacks with freeze-dried cyanobacteria (*Arthrospira platensis*) and green microalgae (*Chlorella vulgaris*) biomass. The freeze-dried algae improved the printability of a snack precursor (batters) (Uribe-Wandurraga et al., 2020).

In a subsequent study, the same algal biomass was added to cookie dough and 3D printed prior to baking at 140 °C. This algae biomass improved the printability of dough and aided the production of 3D objects characterized by high stability and resistance to baking (Uribe-Wandurraga et al., 2021). Because of the inherent instability of valuable cyanobacteria (*Arthrospira platensis*) compounds, Vieria et al. (2020) proposed the encapsulation of cell extract in alginate microbeads before adding it to a cookie precursor (Vieira et al., 2020). This method improved the cookie stability to heat, light, and oxygen during baking and storage. Those very few reports indicate that 3D printing of microalgal food requires further exploration and is likely to develop shortly. With 3D printing, one will be able to shape tasteless and textureless microalgae biomass into a full-featured food product exploiting their high nutritious value.

3. New trends in photoautotrophs-based systems applied in electrochemical processes

Due to rapid climate change, alternative, sustainable, and renewable energy generation and storage methods have gained significant interest. This interest has translated into investigations into the synthesis of new functional materials that may be applied to design complex and effective electrical, photonic, and optoelectronic devices. Due to their unique functions, such as the ability to convert light to energy as well as amplify light signals for metabolic purposes, microalgae and cyanobacteria have become a great inspiration and an alternative, green source in the design of subsequent generation architectures for the electrical and electronic industries (Milano et al., 2019).

In recent years, biophotovoltaics (BPVs) have arisen as a biological method of electricity production by using photosynthetic microorganisms (Chandra et al., 2017; Ng et al., 2021, 2017; Tschörtner et al., 2019; Wey et al., 2019; Zhu et al., 2019). In BPV, microalgae and cyanobacteria can serve as an effective, low-cost, and ecological source of electrical energy because of their photosynthetic activity (**Figure 7A**).

Fig.7.

Figure 7A shows that the photosynthetic algal activity enables the "harvesting" of light which causes electrons to be displaced and thus transferred across the cell membrane to the external environment. This transfer of electrons is manifested as the electrical current which may be used for power generation in bioelectronic devices. Typical biophotovoltaic setups resemble conventional microbial fuel cells, consisting of bioelectrodes inserted into single- or dual-chamber systems (Vinayak et al., 2021). In such setups, the phototrophic organisms typically grow on the bioanode to form biofilm-producing electrons that flow directly or via mediators to the biocathode (Saar et al., 2018; Strik et al., 2010). Since initial development, the efficiency of BPV systems has been constantly improved to reach that of their synthetic counterparts. For example, a significant improvement has been achieved by taking advantage of the synergism between different photosynthetic species (e.g., cyanobacteria and microalgae) incorporated into one BPV system (Chandra et al., 2017). Saar et al. (2018) used genetic engineering to generate cyanobacterial *Synechocystis* sp. cells deficient in photosynthetic and respiratory electron sinks that exhibited elevated exoelectrogenic activity to develop an electron flow gradient as shown in **Figure 7B** (Saar et al., 2018). The study integrated mutant cells into a properly designed microfluidic chip that allowed for flow control and independent charging and power generation optimization. The device showed a power production several times higher than the highest efficiency achieved by any wild-type cell BPV.

In another study by Roxby et al. (2020), the amplification of bioelectricity was investigated via the examination of a new concept of a photosynthetic resonator. The photosynthetic resonator based on the green unicellular microalgae *Chlorella* sp. was designed in a Fabry-Perot microcavity (Roxby et al., 2020). The significant energy coupling between the optical micro/nanocavity mode and photosynthetic resonance could enhance photocurrent generation. The electrical power increased by > 600% and 200 % when the photosynthetic resonator was used in the biomimetic models and living photosynthesis in algae, respectively. Based on the photosynthetic resonator, developed optofluidic devices may offer new possibilities in bioenergy generation, photocatalysis, or sustainable optoelectronics. In the subsequent study, they proposed a novel concept of employing a *Chlorella* sp. living sensor to detect heavy metal ions. The photocurrent was enhanced by nanocavities formed between Cu nanoparticles and the Cu electrode beneath. Heavy and light metal ions in water, including cadmium, iron, chromium, and manganese, were detected by applying a biosensor with a detection limit of 50 nM, which is three times better than the threshold defined by the WHO (Roxby et al., 2020).

Another approach to enhance the efficiency of the photosynthetic process and solar-to-biomass conversion yield was demonstrated by Leone et al. (2021). By *in vivo* incorporation of a molecular antenna (Cy5 organic dye) in diatom microalgae cells (*Thalassiosira weissflogii*), the authors enhanced photosynthetic oxygen generation and cell density by 49% and 40%, respectively. The presented photosynthesis-enhancing method may become an alternative approach to genetic modification-based strategies, which require specific and expensive tools and are limited to several genetically fully sequenced species of diatoms (Leone et al., 2021).

Despite significant progress in improving BPV electrical performance, large-scale production of BPV devices remains challenging. To address this challenge, Sawa et al. demonstrated the feasibility of using a simple commercial inkjet printer to fabricate a thin-film biophotovoltaic cell by creating biological *Synechocystis* sp.-based and nonbiological carbon nanotube patterns onto paper (Sawa et al., 2017) as shown in **Figure 7C**. A hydrogel film covering the electrodes acted as a salt bridge between the anode and cathode and provided a culture environment for the printed cells. The devices continuously produced low-voltage electricity both in the dark and when exposed to light.

In another study, Liu et al. (2018) developed a hybrid biological photovoltaic device using 3D bioprinting for cyanobacteria (*Synechocystis* sp.) encapsulation in hydrogels (Liu et al., 2018). The authors combined bacterial (*Shewanella oneidensis*) respiration with cyanobacterial photosynthesis to continuously produce bioelectricity. The system was designed to maximize syntrophic interactions between microorganisms and prevent their direct physical contact. The device efficiently produced energy over a long-term period without additional organic fuels. The immobilization of microalgae in hydrogels for bioelectronics has another advantage in that it creates biointerfaces. For example, a *Chlorella vulgaris*-containing alginate hydrogel substrate laden with hydroxyapatite was investigated for its usability as a living electrode (Al-Mossawi et al., 2021). The electrode improved the interconnection between inorganic and organic surfaces and exhibited conductivity sufficient to complete an electrical circuit and power LEDs.

An amazing application of photoautotrophs 3D printing has been demonstrated by Joshi et al. (2018). The authors created a bionic mushroom for photosynthetic bioelectricity generation by integrating cyanobacteria (*Anabaena*) to produce electricity, with graphene nanoribbons capable of collecting electric energy (Joshi et al., 2018). Both materials were directly printed onto the umbrella-shaped pileus of a mushroom. This technique allowed creation an anisotropic, densely packed cyanobacterial architecture that exhibited a higher photocurrent than isotropically cast cyanobacteria of similar seeding density. This technique could be adapted to 3D print other bacterial and microalgal strains towards bacterial and photosynthetic nanobionics.

To advance microalgal bioelectronics, several key challenges should be addressed. Genetic engineering may improve the efficiency of photosynthesis and in turn electricity production. Encapsulation techniques need to be optimized to provide an adequate environment for the microorganisms to maintain or even boost their function and the capacity of light-harvesting. Finally, biofabrication technologies should be developed and optimized to allow the mixing of photosynthetic organisms with biomaterials without affecting microalgal functionality.

4. Photoautotrophs in urban space-new perspectives

4.1. Water and wastewater treatment

Microalgae and cyanobacteria have been used in wastewater and water treatment systems for several years (Abdel-Raouf et al., 2012). Due to their excellent biosorption capacity, various algal species are frequently used in municipal and industrial wastewater treatment (Abdel-Raouf et al., 2012). The primary pollutants treated with microalgae and cyanobacteria thus far are organic compounds (CODs), nitrogen, and phosphorus compounds, which are the materials of algal biomass. Despite the many studies conducted on the biosorption, bioremediation, and biodegradation of pollutants from wastewater (Mustafa et al., 2021), researchers are still engaged in further exploration in this area. For example, Bahman et al. (2020) tested the effect of light wavelength on the sorption capacity of *Spirulina platensis*. The study showed an 85–93% and 96–100% removal rate for phosphate and nitrogen in the form of ammonium nitrogen from municipal wastewater (Bahman et al., 2020). In another study, Biswas et al. (2021) used a consortium of photoautotrophic microorganisms mainly *Microcystis aeruginosa*, *Synechocystis* sp. and *Thermosynechococcus elongatus* BP-1 to treat wastewater from the dairy industry. The consortium reduced nitrate concentrations by 91–93%, phosphate by 97–98%, ammonia nitrogen by 80–90%, and organic compounds (COD) by 68–89% (Biswas et al., 2021). While growing, living photosynthetic microorganisms not only effectively remove macronutrients, like nitrogen, phosphorus or COD from the external environment but also metal ions (Masmoudi et al., 2013). Because of the abilities of simultaneous bioaccumulation and adsorption, microalgae may effectively eliminate heavy metals from water resources systems. A paper by Wang et al. (2021) presented the potential for biosorption of cadmium cations from wastewater (the concentration of Cd^{2+} ranged between 2 mg L^{-1} and 30 mg L^{-1}) with the microalgae *Didymogenes palatina*, isolated from a waste tailing mine in Fankou, Shaoguan city, Guangdong Province in China (Wang et al., 2021). The study showed that up to 88% of low concentrations of Cd ions in water could be removed. In another study, it was shown that an NMC (native microalgae consortium), isolated from the wastewater treatment plant, comprised by microalgae: *Tetradesmus* sp. (68% similarity with *Tetradesmus obliquus*.), 29% with *Scenedesmus* sp. and a yeast with 93% similarity, could be used to biosorb up to 99% of Cr(III) ions from wastewater when the concentration exceeded 5 g/L (Moreno-García et al., 2021). Such high removal efficiencies may help to achieve residual levels of metal ions in solutions below the maximum permissible values for water and wastewater (Rawat et al., 2016). Because of the easy cultivation and high biosorptive capacity, microalgae provide a green and efficient way in wastewater treatment for removing heavy metals from industrial and urban sewage.

To date, research on the biosorption of pollutants has mostly focused on removing heavy metals from wastewater of various sources (Salama et al., 2019). However, microalgae and cyanobacteria have the unique ability to absorb toxic metals and capture metal cations from wastewater in addition to converting them into highly valuable particles, e.g., nanosilver (AgNPs). The mechanism of silver ion biosynthesis into AgNPs is not fully understood (Shankar et al., 2016). Metals usually have toxic effects on microorganisms (Masmoudi et al., 2013); however, the biosynthesis of AgNPs by algal species does not demonstrate such effects. Microalgae and cyanobacteria probably accumulate metal nanoparticles in the intercellular space, without affecting the algal life cycle. Alharbi et al. (2020) used dried and ground algae and their aqueous and ethanolic extracts to biosynthesize AgNPs (Alharbi et al., 2020). A study conducted with green microalgae (*Scenedesmus obliquus*) and cyanobacteria (*Spirulina platensis*) demonstrated the ability of algae to biosorb silver ions from aqueous solutions and subsequently reduce the ions to produce AgNPs that may be retained in both dry biomass and extracts (Alharbi et al., 2020). The highest concentration of AgNPs was observed with the ethanolic extract, while the lowest content was achieved with an aqueous solution. Nevertheless, all samples showed high cytotoxicity against HepG2 (hepatocellular carcinoma) and MCF-7 (breast adenocarcinoma) cells (Alharbi et al., 2020). The production of AgNPs has also been observed in other microalgae species such as *Nannochloropsis oculata*, *Dunaliella salina*, and *Chlorella vulgaris* (Mohseniazar et al., 2011). Similar biosynthesis capabilities of AgNPs were demonstrated in wet microalgae biomass collected from the seawater surface in Tuticorin Harbor (India) (Sathishkumar et al., 2019). In the collected wet biomass, mainly a species of cyanobacteria, *Trichodesmium erythraeum,* silver nanoparticles with a cubic shape and average particle size of 26.5 nm were biosynthesized. The produced nanoparticles were cytotoxic against cicatricial strains (*Staphylococcus aureus* and *Proteus mirabilis*) and drug-resistant bacterial strains such as *Escherichia coli* (amikacin), *Staphylococcus aureus* (tetracycline), and *Streptococcus pneumoniae* (penicillin) (Sathishkumar et al., 2019). Biogenic synthesis of silver nanoparticles is advantageous over physical and chemical methods due to the lower cost of reaction-specific parameters and the lack of use of toxic chemicals, and generation hazardous byproducts.

Wastewater treatment plants face a new challenge from emerging pollutants, primarily pharmaceuticals. Changing regulations on the quality of treated wastewater leads to stricter standards for the concentrations of these pollutants discharged to receiving bodies, e.g., rivers. It appears that microalgae also have biosorption potential for these challenging contaminants. Depending on the reaction mechanism and pharmaceuticals in water, these pollutants can be removed entirely from wastewaters using different microalgae species or a consortium of microalgae combined with photosynthetic bacteria (Hena et al., 2021; Vassalle et al., 2020). Treatment plants with high-rate microalgal ponds effectively remove nutrients as compared to classical methods and are more efficient in eliminating diclofenac and antibiotics, with a significant environmental impact (Villar-Navarro et al., 2018).

A further step to exploit the potential of photoautotrophs in water purification was proposed by Serra et al. (2020) (**Figure 8)**. The study presented the possibility of resorting to the photocatalyst in a full circular cycle. The authors developed the Ni@ZnO@ZnS-algal-hybrid photocatalyst system using *Spirulina platensis* species (Serrà et al., 2020) and showed that cyanobacteria mineralized persistent organic pollutants under the influence of sunlight. The process produced clean water and carbon dioxide, which were recycled for further cyanobacteria culturing. By separating the photocatalyst, Ni@ZnO@ZnS was recovered to reconstruct the catalyst, and the separated cyanobacterium biomass was applied for bioethanol production. Simultaneous saccharification and fermentation produced bioethanol without pretreatment, with yields comparable to those obtained from carbohydrate feedstocks. Such a solution facilitates water remediation, the management of the carbon dioxide generated, and the production of an additional product in the form of bioethanol, which is in line with the increasing formulation of zero-waste policies (Serrà et al., 2020).

As it can be seen, although the application of microalgae or cyanobacteria in water and wastewater treatment has been in use for a long time, current technologies require further development. In this context, it is essential to perform further research on water treatment from emerging contaminants and on the modification of existing treatment methods involving photosynthetic microbes to improve their efficiency, economy, and environmental performance.

Fig.8.

4.2. Immobilization for cell protection, stability, and function control

In a more modern approach to microalgae-based biotechnology, the immobilization of cells in hydrogel-based structures is attracting growing attention as it enables the efficient cultivation of photosynthetic microorganisms without disturbing their metabolic functions or sorption capacity. Immobilization is a useful technique for controlling and intensifying microalgae and cyanobacterium processes. Proper immobilization minimizes microorganisms' escape into the surrounding environment, which can otherwise contaminate the natural watercourse. The use of scaffolding materials that are capable of maintaining microorganism functions paves the way for novel applications in environmental engineering and biomedicine. Typical environmental applications of immobilized microalgae and cyanobacteria include removal of contaminants from wastewater and water, fabrication of carbon-capturing systems, development of bioelectrodes and biosensors and production of clean energy, among others (Behl et al., 2020; Gouveia et al., 2014; Haigh-Flórez et al., 2014; Kusmayadi et al., 2020; Ng et al., 2017).

Gel entrapment in natural polysaccharide matrices is the most common immobilization technique for biosorbents and microalgae/cyanobacteria (Moreno-Garrido, 2008; Skrzypczak et al., 2019). Calcium alginate spheres constitute the most common matrices for the storage of cells or active ingredients (Skrzypczak et al., 2019). Some attention has been given to other techniques of producing polymer scaffolds for cells, such as film casting and molding (Al-Mossawi et al., 2021). Cells can be entrapped within the polymeric network during their formulation or physically attached to already prepared scaffolds (Al-Mossawi et al., 2021; Lu et al., 2019). Shaping and patterning of microorganism-containing polymers extend their potential applicability. For example, alginate embedded with *Chlamydomonas reinhardtii* was deposited on various fabrics to manufacture an artificial leaf-like flexible device for hydrogen generation (Das et al., 2015). Hydrogen production was possible due to direct photolysis of water by redirecting microalgae metabolism under anaerobic conditions. The biomimetic device was capable of producing twenty times more hydrogen per gram of algae than batch reactors. Because the system is very efficient and easily scalable, it could replace traditional biofuel production in reactors.

In the bioprinting process, bioinks which are hydrogel precursors made of natural polymers, immobilize cells, before being deposited and solidified. Alginate bioinks are usually biocompatible and support cell growth but demonstrate low printability; hence, they need improvement (Hazur et al., 2020; Jia et al., 2014; Li et al., 2016). Malik et al. (2020) tested various alginate precursors with different viscosity modifiers (κ-carrageenan, methylcellulose, laponite RD®, Curran, Ludox TM-50) as bioinks for robotic extrusion of algae-embedded scaffolds for large-scale applications (Malik et al., 2020). To demonstrate the feasibility of the approach on the macroscale, the authors printed a 1000 × 500 mm fibrous hydrogel panel with different hydrogels and varying water percentages (**Figure 9A**). The *Chlorella sorokiniana* cells remained viable for 21 days after printing the construct, with visible growth during the first 7–10 days of cultivation. Although alginate is one of the most employed biopolymers in bioprinting, silk protein has attracted growing interest as a scaffolding material for cells. Silk protein-based bioinks were used for 3D printing of constructs laden with the green marine microalgae *Platymonas* sp. CBS 152475 (green algae in the family Volvocacea, *Platymonas* genus), Carolina Biological Supply Company (Burlington, NC, USA), for environmental applications (Zhao et al., 2019) (**Figure 9B**). The microalgal cells survived in the polymeric matrix and showed consistent photosynthetic activity for more than 4 weeks.

Fig.9.

Another way to immobilize *Chlorella pyrenoidosa* biomass in a polylactide (PLA)/poly(butylene adipate-coterephthalate)(PBAT) biocomposite, the PLA-PBAT-*Chlorella pyrenoidosa* composite was demonstrated by Xia et al. (2020). In the first step, the authors dried PLA, PBAT, and *Chlorella pyrenoidosa* under vacuum for 12h; next the dried components were premixed on a homogenizer and extruded on a twin-screw extruder with a screw diameter of 22 mm. The resulting filament was then printed on a 3D printer (FDM method) and tested as a methylene blue adsorbent. It was found that a scaffold with a concentration of 30 parts by mass of microalgae was sufficient to maintain good mechanical strength. Studies have indicated the desorption properties of methyl blue from the printed scaffold. 3D printouts were used at least six times, maintaining a 72% decolorization efficiency after the last cycle. Thus, this method has excellent potential in wastewater treatment by biosorption (Xia et al., 2020).

4.3. A new perspective of photoautotrophs application in aquaculture

Aquaculture, or marine animal farming, is a very important and fast-growing segment of the agricultural industry. It provides a large amount of protein for human consumption (Gjedrem et al., 2012). Currently, to protect farmed marine animals from emerging diseases, one of the common solutions is antibiotics. Regrettably, the large-scale use of antiseptic drugs may lead to the emergence of antibiotic resistance. Consequently, various strategies need to be developed to address this problem, the most promising of which is to use microalgae or cyanobacteria as a vaccine carrier (Ma et al., 2020).

The excellent function of microalgae and cyanobacteria is the production of substances (mostly proteins, vitamins, carotenoids, and polysaccharides) with antibacterial activity that protects animals against bacterial infections (Gateau et al., 2017; Joshua and Zulperi, 2020; Koyande et al., 2019). Nontoxic and well-known microalgae such as *Haematococcus lacustris*, *Nannochloropsis* sp., *Chlorella* sp., and cyanobacteria *Arthrospira platensis* are commonly used for this purpose. To create innovative and effective vaccines, gene transfer technologies gave satisfactory results. The research undertaken by Kiataramgul et al. (2020) involved the production of the transgenic green microalgae *Chlamydomonas reinhardtii* that could function as a vaccine carrier (Kiataramgul et al., 2020). In the aforementioned study, the integration of a codon-optimized synthetic WSSV VP28 gene (encoding an envelope protein VP28 of white spot syndrome virus (WSSV)) into the chloroplast genome of microalgae led to creating a suitable system for the delivery of viral antigens. Indeed, the study demonstrated that shrimp fed on the transgenic green microalgae showed the highest survival rates (87%) when exposed to the white spot syndrome virus. In another study, Abidin et al. (2021) created transgenic *Nannochloropsis* sp. as a vaccine carrier to ameliorate vibriosis, the most common disease caused by gram-negative bacteria from the genus *Vibrio* spp. (Abidin et al., 2021). The transgenic microalgae harbored a fragment of the outer membrane protein kinase gene from *Vibrio* spp.. This kinase is a receptor for a broad host range vibriophage KVP40 in members of *Vibrionaceae* and can act as a protective antigen. Therefore, these algal strategies present opportunities for a new, efficient, fast, and less labor-intensive method for the control of diseases in aquatic animals (fishes and shrimp) through oral delivery, hence indirectly protecting humans from vibriosis. This infection can be caused by the consumption of raw or undercooked seafood contaminated by *Vibrio* spp. (Baker-Austin et al., 2018).

There are still some issues in aquafarming, especially in context of polymicrobial co-infection. To date, it is challenging to find potent treatment methods based on oral vaccines from microalgae for multi-pathogen infections, not to mention that the application of genetically engineered microalgae species on a commercial scale is restricted in many countries by law and regulations. Due to concerns associated with unpredictable and unexpected open cultivation of genetically modified microalgae, up to the present time there are no commercial outdoor cultivation of transgenic microalgae species.

Apart from controlled aquafarming, marine aquaculture currently also faces many threats, including overfishing, diseases, and ocean pollution, with rapid climate change constituting the most challenging issue. Especially corals are sensitive to temperature fluctuations. These "underwater rainforests" provide livelihoods for thousands of people and habitats for thousands of marine species (Eddy et al., 2021). Due to global warming, coral reefs have been halved in the past two years. To preserve the survival of this distinctive environment, new and effective solutions are being extensively developed.

One of the most remarkable and unique solutions was proposed by Wangpraseurt et al. (2020), who combined a 3D printing approach with photosynthetic microorganisms to design microalgae-laden hydrogels mimicking coral reefs. Scientists recreated coral tissue and skeleton with micron-scale precision using various biopolymers and hydrogels. Because of the addition of nanocellulose, the scaffolding material simulates the optical and mechanical properties of different coral species. Bionic 3D-printed coral reefs were based on the symbiosis between photosynthetic microalgae (*Symbiodinium* sp.) and the animal host-mimicking material. Artificial corals may become a platform for investigating coral-algal interactions and the photophysiology of different microalgae under *in vivo* conditions to understand the breakdown of this symbiosis during coral reef decline. Such an approach may prevent coral bleaching and reef extinctions in the future.

Marine aquaculture typically has a reduced carbon footprint, which in 2017 was approximately 0.49% of that year's total global anthropogenic greenhouse gases emissions. Thus, it requires less land, energy, and freshwater (Jones et al., 2022). For this reason, it may be an efficient solution for global food demand as it can provide a healthy and sustainable protein source for future populations. On the other hand, coral reefs protect coastlines from breaking tidal waves, storms, and erosion and provide an essential ecosystem for marine life. The future aquaculture is in the same class as sustainable marine production. Sustainability mostly means reef conservation and marine environment protection but it will depend on factors such as policy reforms, technological innovations, and social information (Costello et al., 2020).

4.4. Photoautotrophs in urban architecture

Modern problems of civilization, such as climate change, the depletion of natural resources, and unsustainable crop yields, make it necessary to investigate environmentally friendly solutions for further sustainable development of humanity.

Among them, there are bioregenerative life support systems (BLSSs), which operate on the principle of a self-sustaining bioregenerative ecosystem to meet the basic needs of urban life and while also mitigating climate change (Sreeharsha and Venkata Mohan, 2021). Early concepts of BLSSs date back to the 20th century (Häder and Schäfer, 1994). Solutions to a reduction of its environmental impact have been explicitly sought for recently. The basic functions of these ecosystems include energy capture and conversion, mineral cycling, and extraction of valuable ingredients (Sreeharsha and Venkata Mohan, 2021). Microalgae can readily be employed in such BLSSs to undertake these functions. Indeed, the inherent versatility of microalgae applications makes it impossible to overlook its potential when designing circular economy concepts. Chew et al. (2021) stated that the use of algae plays a vital role in developing green cities since it may contribute to climate neutrality via the mitigation of greenhouse gas emissions and thus prevent temperature rise exceeding the 2 °C threshold (Chew et al., 2021). Investments in bioenergy via microalgae biomass processing in biorefineries for biodiesel, bioethanol, and biogas (methane and hydrogen) production also contribute to greenhouse gas emission control. The authors noted that other materials can be obtained from microalgae, such as, polyunsaturated fatty acids, antioxidants, vitamins, or medicines. Thus, it is fair to say that green cities will not be able to exist without microalgae.

Nowadays, applications of microalgae in urban space have been gaining more attention. In Germany, the world’s first algae-powered house – the *BIQ building* – was constructed, which is the materialization of the idea of an ecological place of residence integrated with panels made of microalgae (IBA Hamburg GmbH, 2013) (**Figure 10A**). The use of microalgal photobioreactors in building façades is currently a very expensive investment, far exceeding the cost of solar and conventional fuel systems. However, as Elrayies notes, the cost-effectiveness of such systems may decrease in the coming years due to the shift away from fossil fuels. The cost of a microalgae façade is in many cases higher than that of conventional elevations, but much more durable, so it is estimated that when converted to current prices, the investment cost could pay for itself in up to 13 years (Elrayies, 2018). There are ongoing studies into the use of microalgae in urban spaces. Research on e.g. “algal windows" that enable a building to reduce its energy consumption has been also extensively carried out (Elrayies, 2018). One of the studies has been conducted in Nantes, France (Pruvost et al., 2016). A photobioreactor with microalgae from *Chlorella vulgaris* species was installed on the south-facing façade of a building. A vertical installation was found to induce specific irradiation conditions, specifically during the summer. Tests showed that the intensity of light inside the building was diminished, compared to other inclination angles of PBR, and was initially considered to be a disadvantage. However, this drawback was found to lead to the most constant year-round operating conditions, thus facilitating proper time and process management. Comparable studies have also been conducted in other parts of the world: USA (Decker et al., 2016; Kim, 2013), Indonesia (Martokusumo et al., 2017), and Italy (Pagliolico et al., 2017). A similar window was designed by Negev et al. (2019), however, two microalgae species were used: *Chlamydomonas reinhardtii* and *Chlorella vulgaris*. The algal windows were compared to conventional windows by measuring the thermal conductivity, visible light transmittance, and solar heat gain coefficient. The study showed that, regardless of the side of the building facade, windows with algae save between 8 kWh/(m^2 year) (east side) and 20 kWh/(m^2 year) (south and west side). Only the northern side showed higher energy consumption as a result of the daily solar radiation that characterizes the Mediterranean climate of Tel-Aviv, Israel. The outline of this project is presented in **Figure 10B**. Besides, algal windows act as photobioreactors producing a significant amount of power improving the profitability of this project (Negev et al., 2019).

Fig.10.

Another solution based on microalgae in urban spaces involved biofilms of microalgae on the needles of common yew in Prague, Czechia, to detect anthropological air pollution (Nováková and Neustupa, 2015). The microalgae biofilms gave rapid responses to increased pollutants of gases such as NO_2 or suspended particulate matter, PM10. This undoubtedly modern way of biomonitoring partially protects the microhabitats of conifers, which are a common microecosystem in highly urbanized cities. It is also possible to apply algal biofilm to other surfaces, equally common in urban areas. Research has been conducted on biofilms on tree bark (Freystein et al., 2008), facades (Gorbushina, 2007), and on synthetic materials, metallic coatings glass, or wood (Görs et al., 2007).

Local activities have also been demonstrated. For example, the “Biophotovoltaics' Moss Table project” (Biophotovoltaics, 2012) designed a table that produces electricity from plants, including microalgae embedded in its structures (**Figure 10C**). Such a table is only at the conceptual stage but can already generate electricity to power smaller electronic appliances, like a digital alarm clock or small lamp. In this case, the resulting piece of furniture has additional utilitarian purposes and may become competitive alternatives to conventional energy sources in the future.

Undoubtedly, microalgae will continue to find applications in urban spaces in the future. Currently, microalgae technologies are still too expensive to be brought into common use. However, humanity is reaching a point in history at which finding alternatives to consumed natural resources will force the implementation of new solutions. Over time, the cost proportion of new and traditional technologies may change, as pointed out by researchers, which will lead to a greater share of investments involving microalgae and quick commercialization.

5. Conclusions and outlook

This review provides an overview of fascinating biomedical, environmental, and electrical engineering applications of microalgae and cyanobacteria. Based on literature examples, we demonstrated the full potential of these self-sufficient, autotrophic microorganisms to revolutionize the food and fuel industries, wastewater treatment plants, urban environments, and medicine. A great advantage of microalgae and cyanobacteria is that they are equally useful when cultivated on a large scale in bioreactors and as single cells constituting controllable microrobots.

The main challenge of future photoautotrophs-based microbotics will be developing safe and sustainable solutions to operate *in vivo*. The successful transfer of such systems into clinical practice will depend on cooperation between scientists, engineers, and physicians. Microrobotic devices will require efficient energy sources or a simple method of remote control. This could be achieved by combining artificial intelligence with robotics to provide full automation and controllability. Recent advancements in functional materials and ongoing miniaturization of devices are a boost to intensive research in this field.

Although very promising, the few reports on the 3D printing of microalgae/cyanobacteria-based hydrogels indicate that this area of research is still in its infancy and needs further exploration. This will eventually lead to the design of novel biobased devices and environmental, biomedical, and electrical engineering systems. For example, inkjet printing may revolutionize microalgae-based bioelectronics because of its ease of scaling up and cost-effectiveness. The association of emerging fabrication techniques and microalgae also paves the way for new drug delivery therapies and tissue engineering strategies. Algal biomaterials have demonstrated applications in wound healing dressings (Chen et al., 2020), surgical sutures (Centeno-Cerdas et al., 2018), organoids (Haraguchi et al., 2017), and photosynthetic respiratory support systems (Yamaoka et al., 2012).

Despite many promising achievements, the clinical applications of photoautotrophs-based biotechnology have several limitations and challenges to overcome (Agarwal et al., 2021). Firstly, photosynthetic organisms need light of an appropriate wavelength to synthesize essential molecules for growth, while visible light penetration within the tissue is limited. Therefore, successful treatment of tissue hypoxia using microalgal systems would require new implantable technological solutions of continuous light supply that do not cause infection or inflammation near the implanted area. Secondly, as foreign organisms, microalgae may provoke immune responses and trigger inflammation. Because algal applications in biomedicine have blossomed out only recently, immunological aspects have not been fully addressed, but some studies have reported no inflammatory responses of microalgae when applied in contact with animal tissues (Chávez et al., 2016). Future clinical trials should include characteristics of the immunological response to guide microalgae-based system design and to gather more information about major clinical consequences of their applications for immune systems. On the other hand, the immune system can mistakenly identify microalgal cells as the enemy lowering the overall therapy efficiency (Agarwal et al., 2021). Cell immobilization and functionalization strategies to create biocompatible hybrid biosystems seem to be the solutions to this issue. Encapsulation also prevents uncontrolled cell escape into the tissue environment making the system controllable. Finally, social vulnerability and hesitancy may impact the clinical translation of microalgae as humans may be afraid of using living microorganisms in clinical therapies. It is, therefore, crucial to inform patients about health benefits and whether they overweigh potential risks.

Algal-inspired biomedical systems remain in the realm of research, but there are many examples of microalgae and cyanobacteria uses in everyday life. Several modern cities worldwide use multifunctional green microorganisms in the urban environment, including for construction sections, photovoltaics, and city-scale architectural installations. Integrating microalgae photobioreactors into building façades can increase their energetic and environmental performance. The energy produced by microalgae can power the whole building (Caporgno et al., 2015). Biological solar cells are low-cost and ecologically friendly alternatives to synthetic power generation systems. In addition to obvious aesthetic value, microalgae-based installations and entire cities may mitigate the global greenhouse effect and stem climate change. Moreover, microalgae and cyanobacteria could be utilized as a sustainable and valuable functional food in response to global hunger and nutrient deficits (Torres-Tiji et al., 2020). Due to the advantageous qualities of microalgae, it is anticipated that future long-duration space missions will rely on microalgae as a source of food, water, and oxygen.

We believe that it will inspire scientists to utilize the beneficial functions of microalgae to develop new green technologies.

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Conflict of interest form

The manuscript titled "New trends in biotechnological applications of photosynthetic microorganisms" by Anna Dawiec-Liśniewska, Daria Podstawczyk, Anna Bastrzyk, Krystian Czuba, Kornelia Pacyna-Iwanicka, Oseweuba Valentine Okoro, and Amin Shavandi has not been either copyrighted or published previously, nor is it under consideration for publication elsewhere. It has been prepared clearly and concisely to suit the format of the journal. All the authors have participated in the preparing of the manuscript, have read and approved the final version, and agreed that the text should be submitted to Biotechnology Advances. This work was supported by the Polish National Science Centre (grant number 2016/21/D/ST8/01713).

Index of Figures:

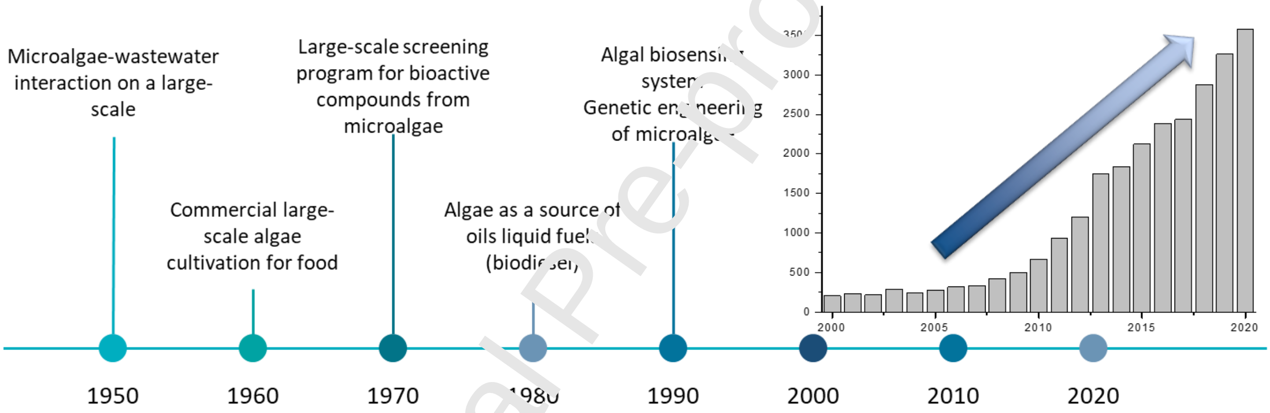

Figure 1. Timeline and milestones in microalgal research development and the expansion of the microalgae literature (26102) in the last 20 years (2000-2020). Source: Scopus database.

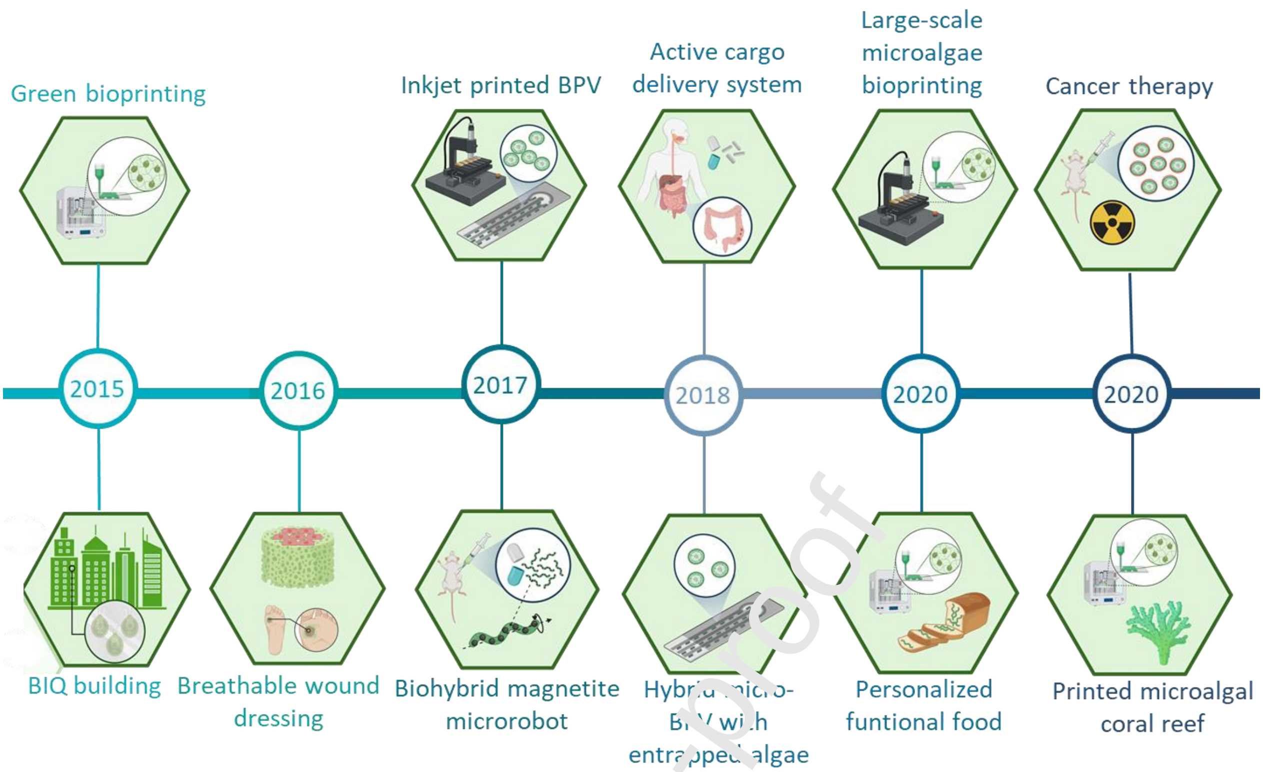

Figure 2. Timeline for some novel advances such as green bioprinting, breathable wound dressing, microrobot, active cargo delivery system, bioinspired multifunctional therapeutic tool, inkjet printed BPV or BIQ building in the applications of microalgae and cyanobacterium cells in the past five years.

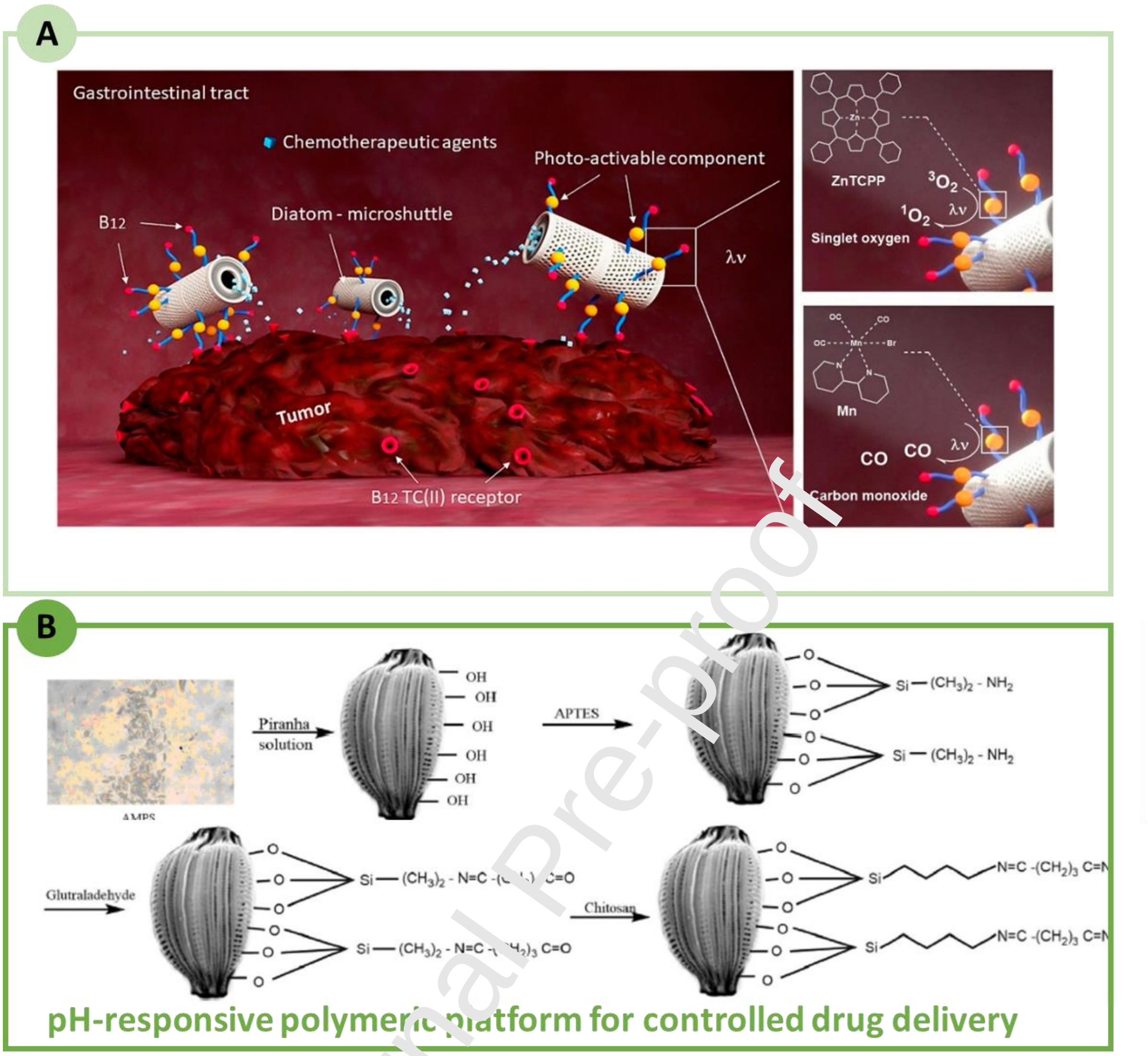

Figure 3. **(A)** Concept of the new drug delivery systems based on microalgae diatoms colorectal cancer treatment, microshuttles modified with photoactivatable unites (yellow spheres) linked to vitamin B12 (pink spheres), and with loaded drugs (blue spheres) are anchored to the tumor cells. The photoactivation additionally induced the generation of toxic CO and $^1O_2$. **(B)** Functionalization of the *Amphora subtropica* frustules (AMPS) with chitosan molecules using 3‑amino propyltriethoxysilane (APTES) and cross-linker – glutaraldehyde. Modified and reprinted with permission from **(A)** (Delasoie et al., 2020) Copyright 2021, MDPI, Basel, Switzerland; **(B)** (Sasirekha et al., 2019) Copyright 2019, Elsevier.

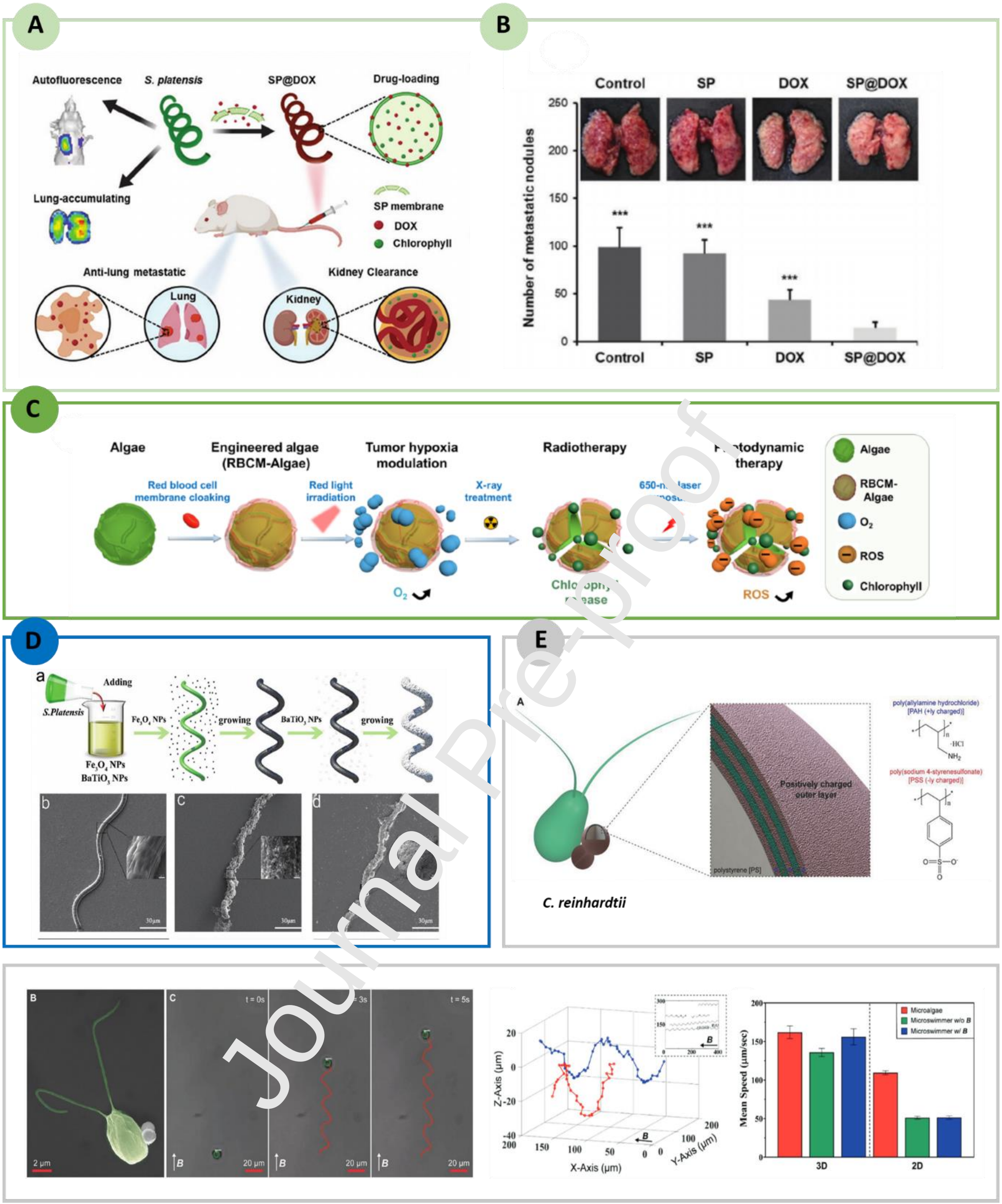

Figure 4. The conception of the microswimmers based on the microalgae and cyanobacterium. **(A)** Schematic illustration of SP@DOX mediated lung-targeted drug delivery and fluorescence imaging-guided chemotherapy to suppress the lung metastasis of breast cancer. **(B)** Representative photographs and the mean metastatic nodules of lung tissues at 5 d in different groups. **(C)** in situ–generated oxygen through microalgae (*C. vulgaris*)-mediated photosynthesis. **(D)** **S**chematic illustrations of surface magnetization of *S. platensis*. **(E)** Overview of the layer-by-layer polyelectrolyte deposition onto spherical magnetic polystyrene microparticles and fabrication

of the microswimmers utilizing electrostatic interactions between the microalga and the functionalized microparticles. SEM image (pseudocolored green, *C. reinhardtii*) of an example algal microswimmer. Example of 2D propulsion trajectories of an algal microswimmer under 26 mT uniform magnetic field. Example the algal microswimmers steered in the x-direction. 2D and 3D mean speeds of the microalgae and the algal microswimmers. Modified and reprinted with permission from **(A)-(B)** (Zhong et al., 2020a), Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; **(C)** (Qiao et al., 2020), Copyright 2020, American Association for the Advancement of Science; **(D)** (Liu et al., 2020), Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; **(E)** (Yasa et al., 2018), Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

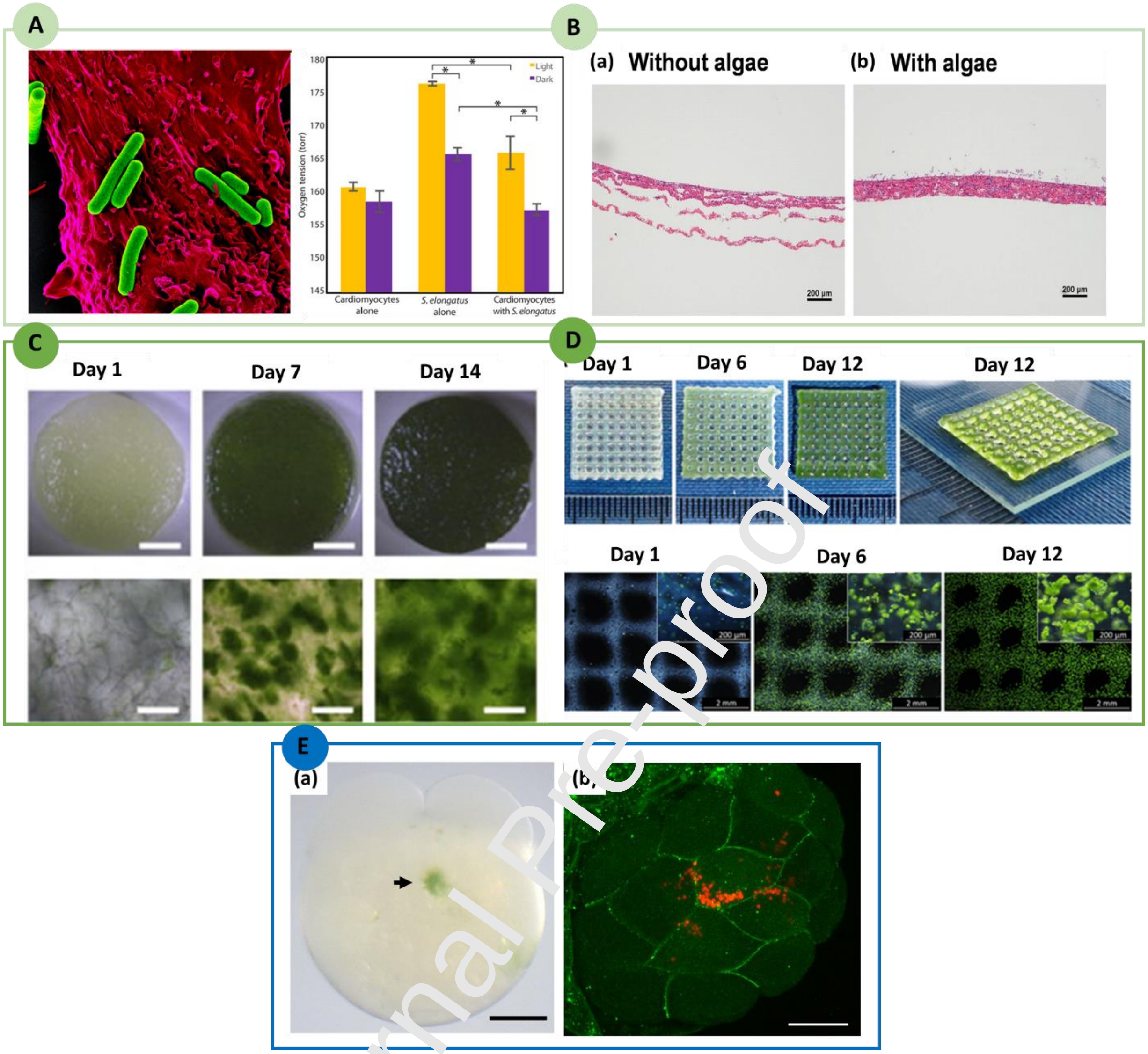

Figure 5. Oxygen-release hybrid biomaterials based on photosynthetic microorganisms used in the creation of bioartificial “breathing” tissues **(A-D)** as well as a chimerical plant-vertebrate organism **(E)**. **(A)** and **(B)** correspond to bioartificial cardiac tissue where mammalian cells such as rat cardiomyocyte cells with *Synechococcus elongatus* cyanobacterium**(A)** and neonatal rat cardiac cells/mouse myoblast cells with *Chlorococcum littorale* microalga in the form of multilayered cell sheet **(B)** were co-cultivated, respectively; **(A)** Presents false-colored scanning electron micrograph of multiple cyanobacteria with a single rat cardiomyocyte (red); **(B)** Presents histological observation of five-layered cardiac cell sheets without (a) or with (b) the microalgae after a 3-day cultivation. **(C)** and **(D)** shows biocompatibility of microalgae with the hydrogel scaffold; **(C)** Co-culture of NIH-3T3 fibroblasts cells and **(D)** SaOS-2 human cells with *Chlamydomonas reinhardtii* microalgae to contract bioartificial skin. **(E)** Chimerical organism (a)-microinjection of *Chlamydomonas reinhardtii* into the zebrafish yolk; (b)-distribution of *Chlamydomonas reinhardtii* in the early

zebrafish embryos. Modified and reprinted with permission from **(A)** (Cohen et al., 2017), Copyright 2017, American Association for the Advancement of Science; **(B)** (Haraguchi et al., 2017) Copyright 2017, Springer, Nature; **(C)** (Hopfner et al., 2014) Copyright 2014, Elsevier; **(D)** (Lode et al., 2015), Copyright 2015, WILEY-VCH; **(E)** (Alvarez et al., 2015), Copyright 2015, PLOS ONE.

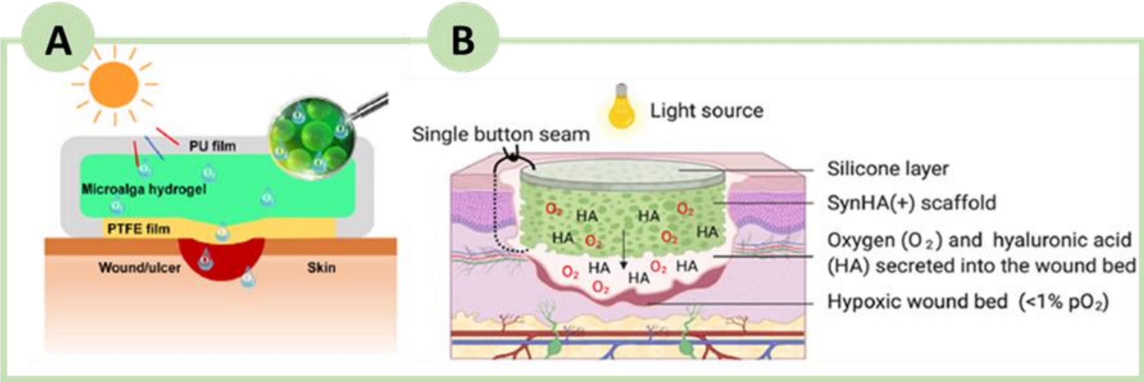

Figure 6. Schematic illustrations of the algae-based wound dressings, **(A)** Simplified figure of cyanobacterium-hydrogel matrix capured in the polyurethane film and polytetrafluoroethylene membrane **(B)** Schematic illustration of the SynHa(+) photosynthetic scaffolds based on fibrin-collagen hydrogel that can be used to treat chronic wounds. Modified and reprinted with permission from **(A)** (Chen et al., 2020), Copyright 2020, American Association for the Advancement of Science; **(B)** (Chávez et al., 2021) Copyright 2021, Elsevier.

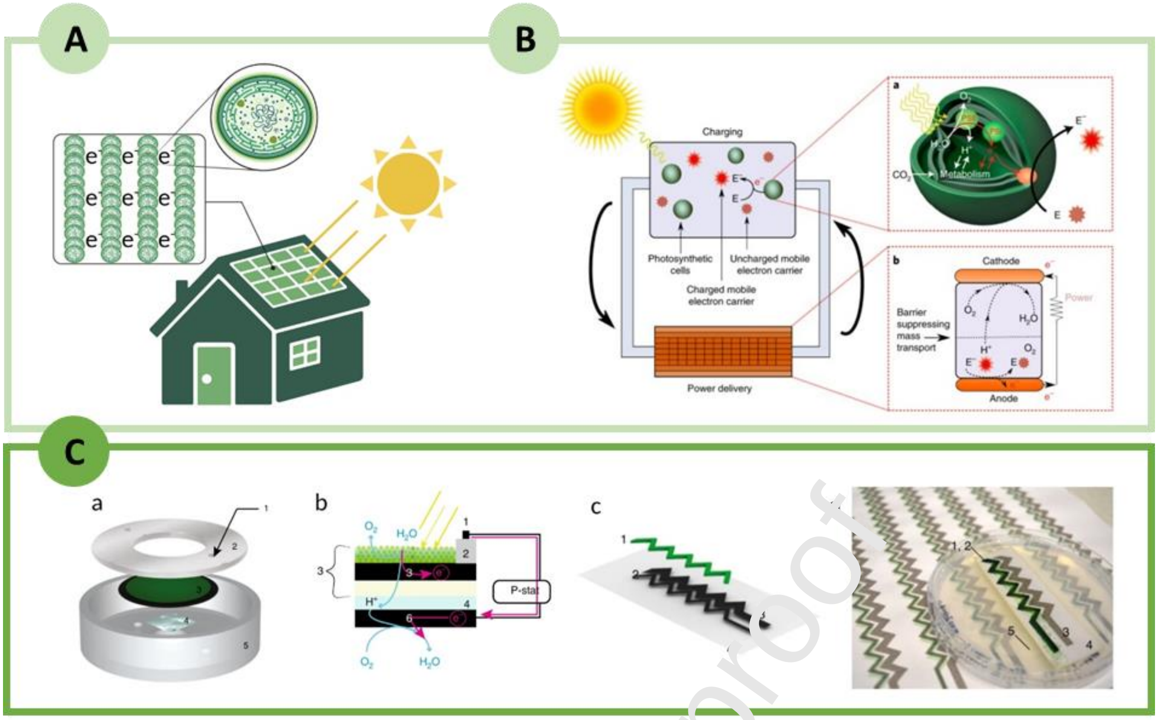

Figure 7. Algae-based electrical systems. **(A)** Scheme of biological photovoltaics; **(B)** Concept of a microfluidic-based BPV system. The device comprises (a) the charging unit with mutant cyanobacteria as biological electricity generators and (b) the power delivery unit. Reproduced from (Saar et al., 2018). The system was innovatively designed to spatially decouple units from another so they can operate independently; **(C)** Inkjet printing of a BPV system. Concept of (a) the BPV unit (b) and its cross-section, where cyanobacteria paths were printed on a paper-based anode; (c) Concept of the digitally printed cyanobacteria-based bioelectrode; (d) A photograph of bioarrays with freshly printed phototrophic cell patterns, and those incubated an agar plate for 3 days. Reproduced from (Sawa et al., 2017).

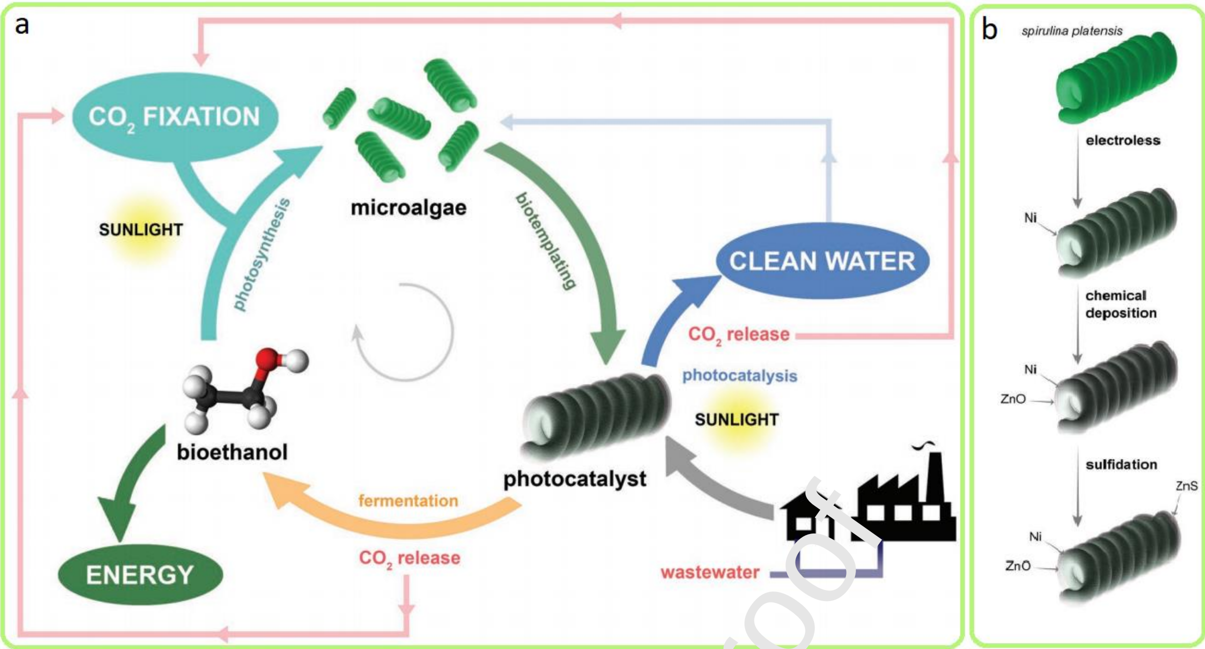

Figure 8. Schematic illustration of the circular process using cyanobacterium (*Spirulina plantensis*) for water mineralization and bioethanol production. (Serrà et al., 2020) © 2019 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

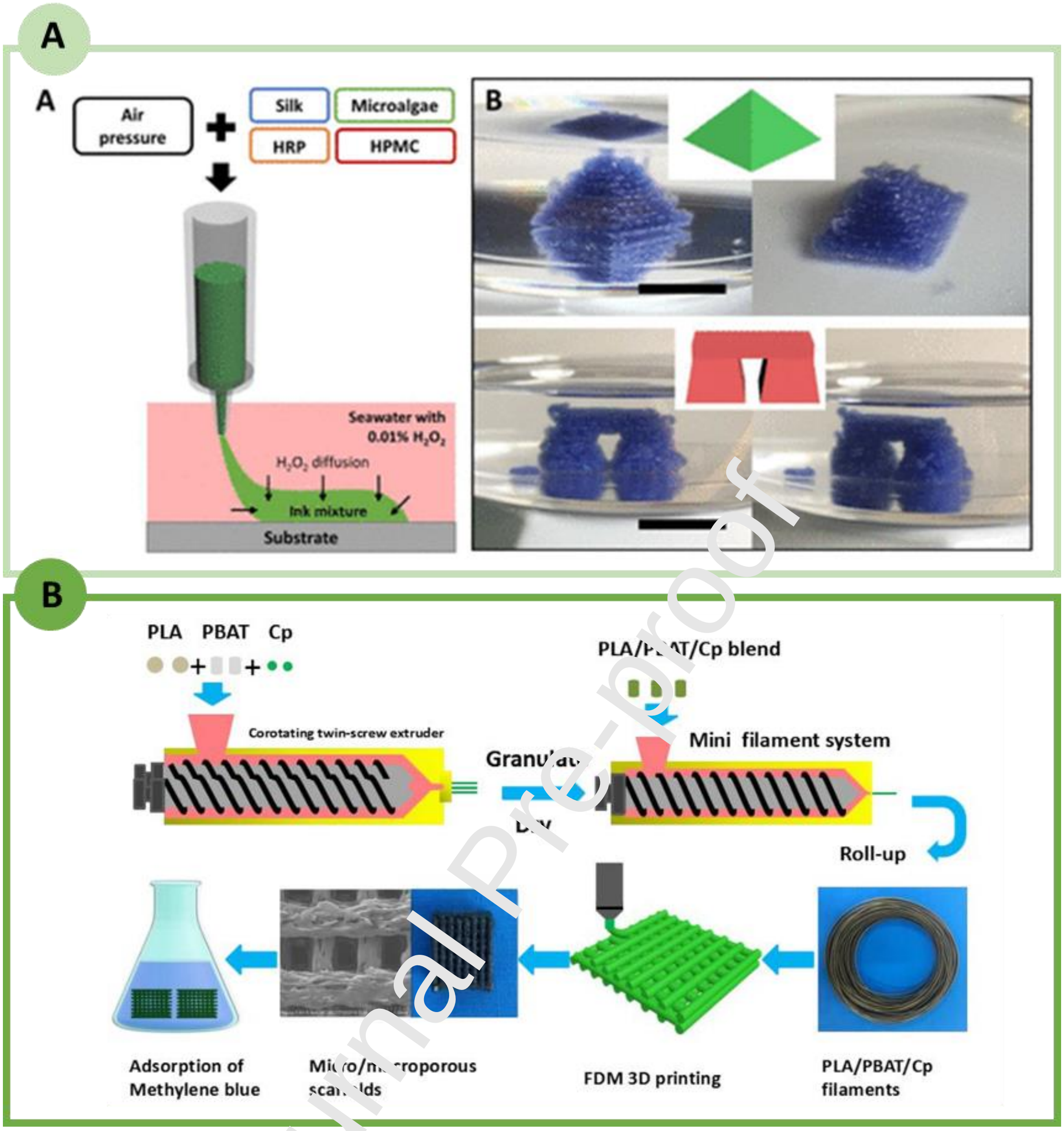

Figure 9. Examples of microalgae immobilization by 3D bioprinting techniques for potential environmental applications **(A)** (a) Schematic illustration of 3D bioprinting process of silk/HPMC/microalgae ink mixtures, (b) 3D printed structures- a square-based pyramid and a bar spanning two conical shaped pillars. **(B)** The schematic diagram for filament preparation based on polylactide/poly(butylene adipate-coterephthalate) (PLA-PBAT) and microalgae *C. pyrenoidosa* biomass (Cp) and composite scaffolds 3D printing. Modified and reprinted with permission from **(A)** (Zhao et al., 2019), Copyright 2019, American Chemical Society **(B)** (Xia et al., 2020), Copyright 2020, Engineered Science Publisher.

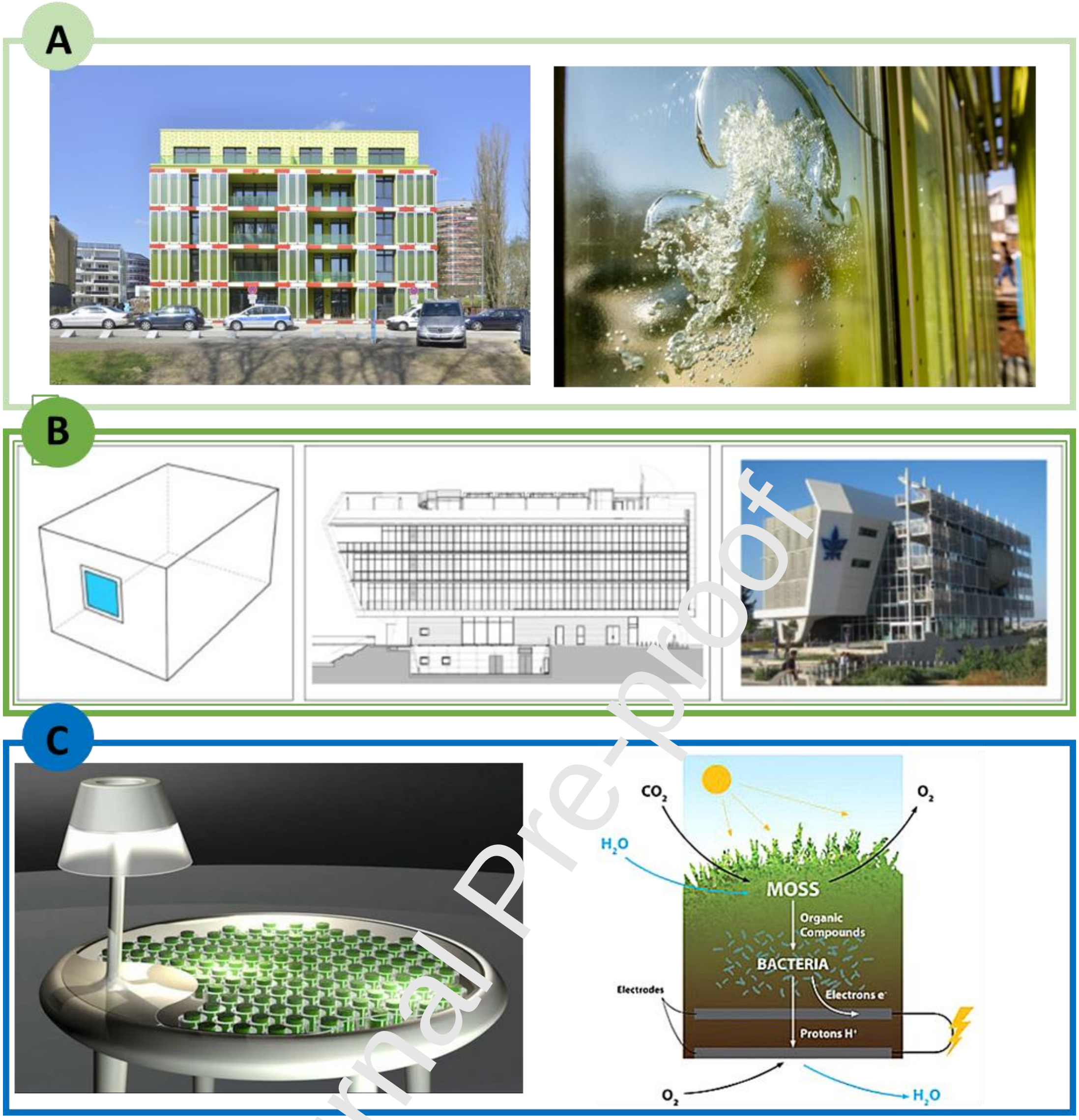

Figure 10. **(A)** The world's first BIQ building with south-facing facades producing energy thanks to microalgae (Fot. IBA Hamburg GmbH/Martin Kunze (left), Fot. IBA Hamburg GmbH/Johannes Arlt Smart (right)) (IBA Hamburg GmbH, 2013) **(B)** Studied simulated "Algal Window" at PSES building at Tel-Aviv University, Israel (Negev et al., 2019) Copyright 2019, Elsevier **(C)** A schematic concept showing the process of converting microalgae into bioenergy; project of "Biophotovoltaic Moss Table" (Biophotovoltaics, 2012).

Index of Tables:

Table 1. Examples of microcarriers based on microalgae biosilica in drug delivery systems.

Species	**Surface modification**	**Targeted substances/Drug release**	**Co-cultivated cells**	**Application**	**References**
Diatomaceous earth (DE) belonging to *Aulacoseria sp.*	Adsorption of dopamine modified Fe_3O_4 nanoparticles onto the diatom surface	Indomethacin/after 12 weeks – 100%	-	Magnetically guided micro-carriers for drug delivery	(Losic et al., 2010)
Diatomaceous earth (DE)	Attachment of graphene oxide sheets on the aminated DE surface by covalent bond or electrostatic interaction	Indomethacin/after 5 weeks – more than 90%	-	Advanced drug delivery systems	(Kumeria et al., 2013)
Diatomaceous earth (DE) belonging to *Aulacoseira sp.*	The aminated diatom surface covered with vitamin B_{12}	Cisplatin, 5-fluorouracil (5-FU), and a tris-tetraethyl[2,2′-bipyridine]-4,4′-diamine–ruthenium(II) complex/ after 4hrs – more than 90%	Colorectal cancer cell line HT-29 and breast cancer cell line MCF-7	Targeted delivery of water insoluble inorganic complexes to tumor tissues	(Delasoie et al., 2018)
Amphora subtropica	The aminated diatom surface grafted with chitosan	Doxorubicin	A549 human lung cancer cell	Drug delivery system to cancer cells	(Sasirekha et al., 2019)
Diatomaceous earth (DE) belonging to *Aulacoseira sp.*	The aminated diatom surface covered with hybrid of vitamin B_{12} photoactivatable molecules	Rhenium(I) tricarbonyl anticancer complexes/ after 5 days – more than 90%	HCT-116 colorectal cancer cells	Colon-focused drug delivery systems	(Delasoie et al., 2020)
Aulacoseria genus	Silanization and decoration of diatom with CTAB functionalized Au NPs	Gentamicin/after 10 days – 93%	-	Drug delivery systems, bioimaging, and nanosensors	(Briceño et al., 2021)

Table 2. Characteristics of microrobots with potential application in medicine.

Species	**Microswimmers construction**	**Targeted substance**	**External Forces**	**Mean velocity [μm s^{-1}]**	**Co-cultivated cells**	**Test in vivo**	**Application**	**References**
Chlamydomonas reinhardtii	Terbium-incorporated green algae (by incubation of microalgae in terbium-rich media)	-	Magnetic field	In dark condition: Untreated: 23.4±4.5 Treated: 21.7 ± 7.1	Green algae with MCF-7 breast cancer cell line and NIH3T3 mouse fibroblasts – biocompatibility tests	-	Drug delivery and/or drug screening systems for potential cancer treatments	(Santomauro et al., 2018)
Chlamydomonas reinhardtii	Polyelectrolyte (PAH and PSS)-functionalized magnetic spherical cargoes (1 μm in diameter) are attached to the surface of the microalgae	Fluorescent isothiocyanate (FITC) labeled dextran - loaded into the PE-functionalized PS microparticles	Magnetic field	**2D:** Bare: 109.54 ± 2.59 Biohybrid: 51.44 ± 2.16 **3D:** Bare:162.05 ± 7.58 Biohybrid: 156.13 ± 9.66	Green algae with cervical cancer (HeLa) cells, ovarian cancer (OVCAR-3) cells, and healthy cells (NIH 3T3) – cytotoxicity tests	-	Active cargo delivery system	(Yasa et al., 2018)
Chlamydomonas reinhardtii	Formation of a thin and soft uniform coating layer consisting of cationic chitosan and iron oxide NPs at green algae surface	Doxorubicin conjugated to NPs by a photocleavable linker (release upon UV light (365nm))	Light exposure	Bare: 109.2±1 Biohybrid: 67.1±0.1	Breast cancer cells were incubated with biohybrid - anti-tumor efficiency	-	Active cargo delivery system	(Akolpoglu et al., 2020)
Chlamydomonas	Chemical modification of the	Vancomycin	-	-	-	-	Active cargo delivery	(Shchelik et al.,

reinhardtii	microalgae surface with dibenzocyclooctyne and vancomycin azide derivatives.						system in skin and soft tissue infections	2020)
Chlamydomonas reinhardtii	Functionalized PS microparticles were attached to the green algae surface	AcN(4-hydroxyproline)10-4-[4-(1-aminoethyl)-2-methoxy-5-nitrophenoxy]-butanoic acid (NPOP)-Ax-Arg peptides linked to PS via amine group	Light exposure	Bare: 112.38 Biohybrid: 83.8	-	-	Microcargo traverse/delivery system for long-distance transportation	(Xie et al., 2021)
Spirulina platensis	Cyanobacteria coated with magnetite NPs	Phycocyanin - substances released during algae degradation	Magnetic field	<u>In water:</u> After 6-/24-/72-hour dip-coating treatments was c.a. 40, 80 and 90, respectively	Algae with 3T3 fibroblast cells, SiHa cervical cancer cells and Hep G2 liver hepatocellular carcinoma cells – cytotoxicity test	The subcutaneous tissue and the intraperitoneal cavity of nude mice	Innovative therapies for cancer treatment	(Yan et al., 2017a)
Spirulina platensis	Cyanobacteria coated with magnetic Fe_3O_4 and piezoelectric $tBaTiO_3$ NPs	$tBaTiO_3$ NPs – piezoelectric stimulation of neural cell upon ultrasound treatment	Magnetic field	<u>In serum:</u> Biohybrid: 333.3	Modified algae culitivated with neural stem-like PC12 cell - cells simulation tests and cytotoxicity test	-	Micromotors for precise neuronal regenerative therapies	(Liu et al., 2020)
Spirulina platensis	Cyanobacteria coated with magnetic Fe_3O_4 NPs and deposited polydopamine (PDA)	PDA – enhanced the photoacoustic signal and photothermal effect	Magnetic field	-	-	Tested in a mouse subcutaneous MDR KP infection model	Treatment of pathogenic bacterial infection	(Xie et al., 2020)
Spirulina	Cyanobacteria with loaded	DOX	-	-	Algae with 4T1 cells	Tested in a mice	Microplatfo	(Zhong et al.,

platensis	bioactive compound				and CT26 cells - anti-tumor efficiency	with injected 4T1-luc cells	rm for lung-targeted delivery and fluorescence imaging-guided chemotherapy on lung metastasis of cancer	2020a)
Spirulina platensis	Cyanobacteria coated with Fe_3O_4 nanoparticles	in situ generated- O_2	Magnetic field	In water: 7[illegible]3	Algae with SKOV3 ovarian cancer cells, 4T1 breast cancer cells, CT26 colon cancer cells- cytotoxicity test; with HEK293 kidney cells and Hepl hepatocyte cells - biosafety tests; with 4T1 cells - oxygen-releasing capability test	Tested in a 4T1 tumor-bearing mice	Treatment of hypoxic cancer	(Zhong et al., 2020b)
Chlorella vulgaris	Microalgae coated with red blood cell membrane (RBCM)	in situ generated-O_2	-	-	-	Tested in a 4T1 tumor-bearing mice	Treatment of hypoxic cancer	(Qiao et al., 2020)
Chlorella vulgaris	Microalgae coated with SiO_2 shell	in situ generated-O_2	-	-	Microalgae with: 293T cells - biocompatibility test and with 4T1 cells - oxygen-releasing	Tested in a 4T1 breast tumor-bearing mice	Treatment of hypoxic cancer	(Li et al., 2020)

					capability test			
Chlorella vulgaris	Microalgae coated with calcium phosphate shell	in situ generated-O_2	-	-	Microalgae with 4T1 cells - cytotoxicity test and oxygen-releasing capability test	Tested in a 4T1 tumor-bearing mice	Treatment of hypoxic cancer	(Zhong et al., 2021b)

Table 3. Microalgae species employed for oxygenation in bioartificial tissue engineering.

Species	**Type of "green tissue"**	**Cultivation method**	**Co-cultivated cells**	**Biomedical application**	**References**
Chlorella sorokiniana	Bioartificial pancreas	Encapsulation in alginate-based hydrogel	Mice pancreatic islets and microalgae	Bioartificial tissues, cell biology	(Bloch et al., 2006)
Chlorella vulgaris	Preservation of the rat pancreas after DCD	*Chlorella* was cultivated in the gas permeable pouch, which was placed in the rat peritoneum	-	Photosynthetic respiratory support, Transplantation	(Yamaoka et al., 2012)
Synechococcus elongatus	Bioartificial cardiac	Dulbecco's modified Eagle's medium with 10% fetal bovine	Rat cardiomyocytes cells and	Ischemic heart disease, myocardial	(Cohen et al., 2017)

(cyanobacterium)	tissue	serum (FBS) under both light and dark conditions	cyanobacterium	infarction	
Chlorococcum littorale	Bioartificial cardiac tissue	Three-dimensional (3-D) tissue; multi-layered rat cardiac cell sheets	Neonatal rat cardiac cells/mouse myoblast lines and microalgae	Cell biology, tissue engineering, regenerative medicine	(Haraguchi et al., 2017)
Chlamydomonas reinhardtii	Bioartificial skin	Immobilization in collagen-based scaffold	NIH-3T3 fibroblasts cells and microalgae	Photosynthetic bioartificial tissues, dermal regeneration	(Hopfner et al., 2014)
Chlamydomonas reinhardtii	Bioartificial skin	Bioprinting of 3D alginate-based scaffolds	The human cell line SaOS-2 and microalgae	Cell transplantation, regenerative therapies	(Lode et al., 2015)
Chlamydomonas reinhardtii and *Chlorella sorokiniana*	Bioartificial skin	Bioprinting of 3D alginate-methylcellulose based scaffolds		Bioengineering	(Krujatz et al., 2015)
Chlamydomonas reinhardtii	Bioartificial tissue	Bioprinting of 3D cellulose- and gelatin methacryloyl-based blend scaffolds	HepG2 cells and murine C2C12 myoblasts and microalgae	Photosynthetic bioartificial tissues	(Maharjan et al., 2021)
Chlamydomonas reinhardtii	Chimerical plant-vertebrate organisms (plantebrates)	Creation of a chimerical organism by injecting microalgae into early-stage zebrafish embryos	Fish-alga chimera organism	Bioengineering	(Alvarez et al., 2015)

Graphical abstract:

Highlights:

- Current trends and prospects in microalgae-based systems and devices are presented
- Microalgae can be used in a broad range of biotechnological applications
- Microalgae-based biomedical and pharmaceutical applications are highlighted
- Emerging biofabrication techniques allow for tuning specific microalgal functions